Volume XX Number 1

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DISEASES OF THE NERVOUS SYSTEM

A Practical Journal on Psychiatry and Neurology

JANUARY
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(CONTENTS ON PATE 6)

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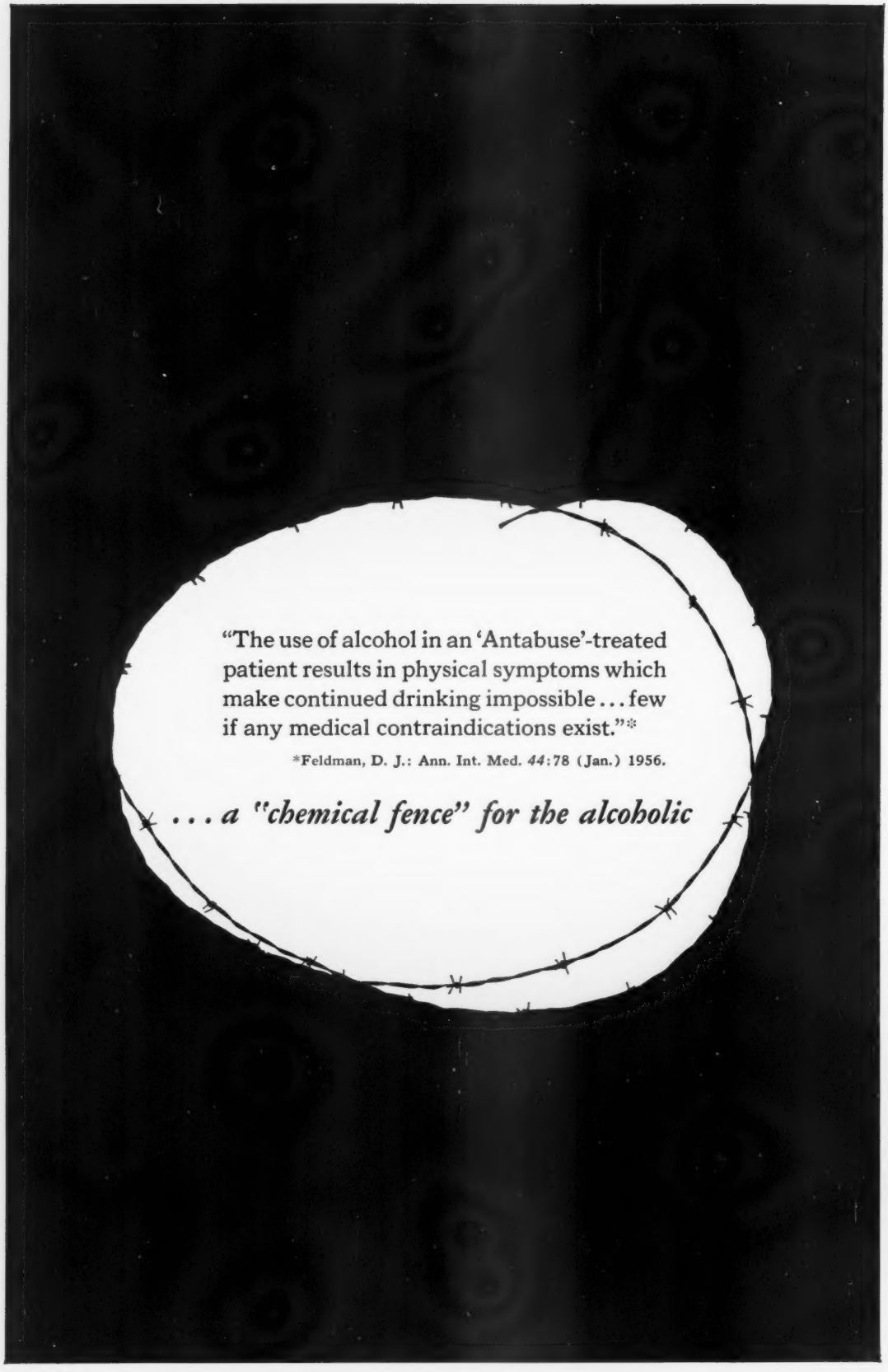
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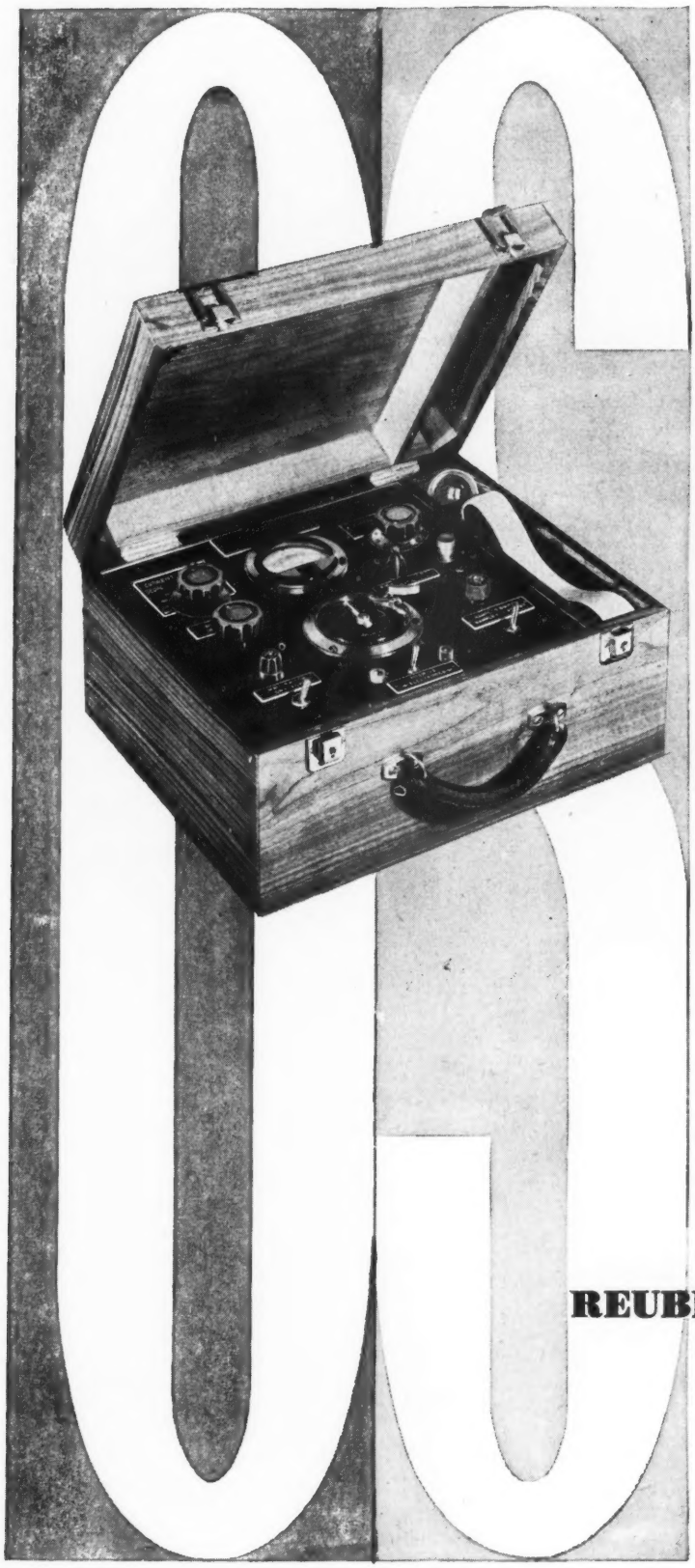

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2. R. S. Schwab, K. E. Osserman and J. E. Tether, **J.A.M.A., 165**:671, 1957.

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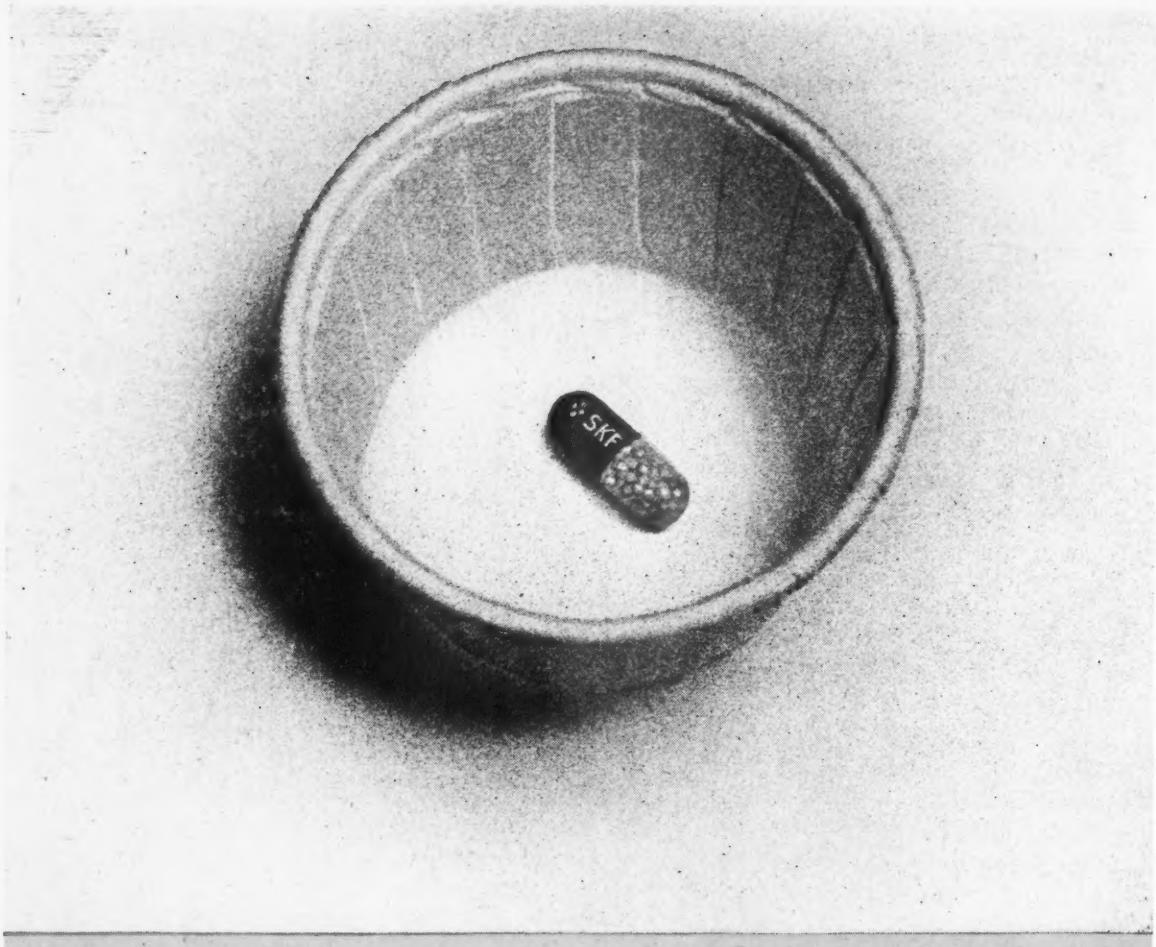

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DISEASES *of the* Nervous System

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

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Migraine and Seizure States in Children

CARY SUTER, M.D., WALTER O. KLINGMAN, M.D., HARRY AUSTIN, M.D., and O. W. LACY, PH.D.

This is a report of a study of 55 cases of migraine seen in children referred to the Seizure Control Clinic of the University of Virginia Hospital during a two year period from January 1, 1955 to December 31, 1956. Since the clinic is primarily for the diagnosis and treatment of epilepsy, these patients were referred with a tentative diagnosis of a seizure state, and in 33 cases definite seizures either of a focal, grand mal, or petit mal type had occurred at one time or another. In 22 cases no positive history of seizures could be obtained and a diagnosis of migraine alone was made. During this period a number of other children with seizures were seen who complained of headache or other symptoms which might be a part of a migraine syndrome, but a definite diagnosis could not be made in these cases and they were not included in this study. These 55 cases were seen during a period when approximately 1,000 children attended the Seizure Control Clinic. This suggests that at least 5.5 per cent of children seen in the clinic for epilepsy may have a migraine syndrome and that 3 to 4 per cent of children with seizures also have migraine.

The findings in these 55 cases have been summarized in the following tables in which are made comparisons between the 33 cases with both seizures and migraine and the 22 cases of migraine without seizures.

As can be seen from Table 1, 30 of the patients were female and 25 were male, with no difference obtaining between the group with seizures and migraine and the group with migraine alone.

The age of onset of migraine attacks was not significantly different between the group with migraine and seizures and the group with migraine alone. Of the 55 cases 28, or approximately 50 per cent began between birth and the sixth year. Eighteen began between 6 and 11 years of age and nine between 11 and 15 years of age. In 11 patients or 20 per cent of the total, attacks began during or before the second year. In the patients with seizures the convulsions usually occurred sometime after the beginning of migraine symptoms, though at times the two occurred at approximately the same age. In two cases the only seizures recorded were so-called febrile convulsions in infancy with the migraine syndrome beginning later.

The frequency of attacks of migraine was so variable that no accurate tabulation is possible. In general, however, the patients could be divided into three groups. One group showed infrequently recurring attacks of migraine over a fairly long period of time, such as an attack every one to six months. Another group showed a period of one month to a year when migraine attacks were very frequent, ranging from daily to once a week. These patients usually showed a period before and after when they had less frequent, but similar attacks. Often this period of increased frequency was associated with some rather obvious psychological stress. Finally, the third group experienced severe attacks of migraine syndrome, with severe vomiting, which might last for as long as a week, these individual, prolonged episodes occurring at relatively infrequent intervals of one to 12 months.

In the group of patients with seizures, the

From the Department of Neurology and Psychiatry, University of Virginia School of Medicine, Charlottesville, Virginia.

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frequency of seizures is remarkable because in at least 75 per cent of these cases, the total number of seizures has been 10 or less; and in the relatively few patients who had more attacks, the episodes have usually been concentrated in a relatively short period of time, varying from three months to two years. In only two patients have seizures continued over a number of years with any frequency. One of these, in addition to migraine attacks, had typical psychomotor seizures and has had a temporal lobe focus in the electroencephalogram on repeated recordings. This patient suffered a rather severe trauma to the head shortly before the onset of seizures. The other patient with continuing seizures has typical petit mal attacks, these occurring apparently without relationship to the migraine episodes and showing the typical petit mal electroencephalographic pattern.

At least one electroencephalogram was recorded in 49 of the 55 cases. Of these 21 were normal and 28 abnormal. There was a significantly greater frequency of focal abnormalities in the electroencephalograms of the group with seizures. While approximately one-half of the patients with migraine alone, in the group having EEG's recorded, showed abnormalities, nearly two-thirds of the group with seizures showed such abnormality. Not only were there fewer abnormal EEG's among the patients with migraine alone but these were also not as abnormal and did not show any definite focal abnormality except in one case (Fig. 1). A few of the patients with seizures who showed focal EEG changes have been followed with serial tests and in some of these focal abnormality has disappeared (Fig. 2), while in others it has persisted. With the disappearance of the focal abnormality there has always been a similar improvement in the clinical situation.

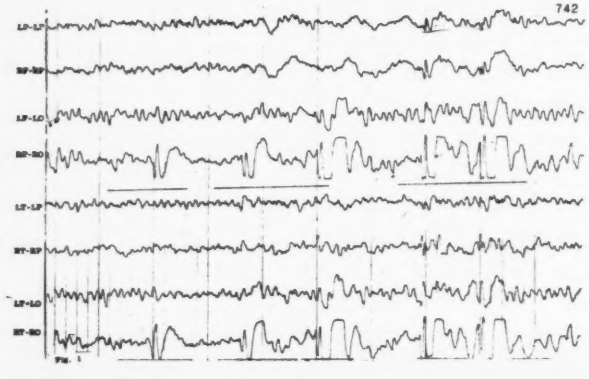

Fig. 1. Focal abnormality (Right occipital parietal dysrhythmia) in EEG of patient with migraine alone.

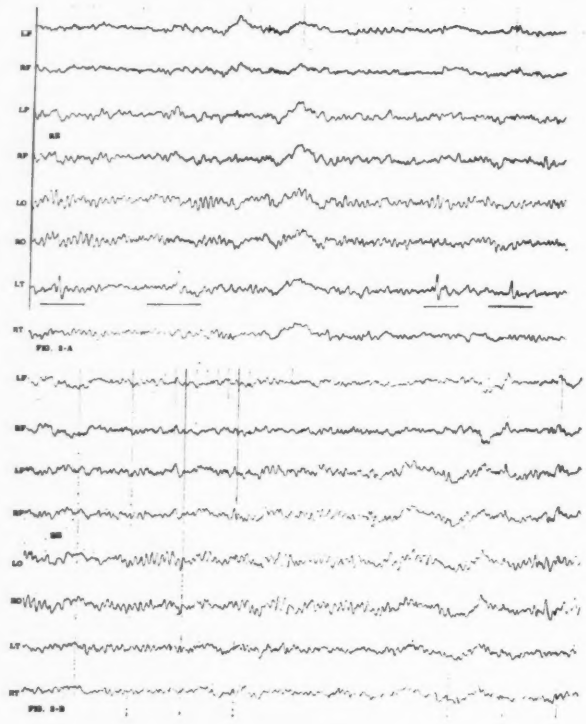

Fig. 2-A. Left temporal lobe spike discharge in EEG of patient with prolonged (2-3 days) attacks of headache, nausea and vomiting, fever, lethargy, and at times generalized convulsions.

Fig. 2-B. EEG of same patient on phenobarbital and after freedom from attacks for one year.

It is of interest that only one patient out of the 55 showed a typical generalized paroxysmal dysrhythmia of the three per second spike and wave type, and thus is the only case which could be said to have so-called centrencephalic type seizures. This finding is of importance because this type of seizure state and seizure discharge is that most often associated with a family history of epilepsy. A review of the family history showed a particularly large number of positive family histories for migraine in the entire group of patients—36 cases or 65 per cent having such a positive family history. There is no difference between the percentage of family history for migraine in the patients with seizures and those without them. On the other hand there is a relatively low percent-

age of family history of epilepsy, there being only seven such positive family histories in the entire group, five of these among the 33 patients with seizures and two among the 22 with migraine alone.

In both groups the effect of a disturbed emotional situation was evident as a precipitating factor, both of individual attacks and of a series of frequent attacks of migraine. The part psychological factors play in bringing about the actual seizure episodes is not evident, but in slightly more than two-thirds of the cases strong psychic influences appear to be at work. Among the 55 cases there were 31 in which there was a particularly upset emotional situation. In 12 of these there was a problem with both the home and school; in 12 cases there was primarily a home problem; and in 7 cases primarily a school problem. In nine of these 31 cases the emotional situation involved a broken home. In some cases improvement of symptoms was associated with the patient's removal from a difficult family or school situation. Though some of the patients were referred to mental hygiene clinics and received psychotherapy, in general, more dramatic results seemed to occur from a major situational change as change in foster home or a change in the school or the teacher. Several of the patients with only migraine were incapacitated to the point that they could not attend school.

As for the symptoms primarily associated with migraine attacks, the most common were, of course, headache, nausea, and vomiting, since the presence of at least one of these was used as a criterion for a diagnosis of migraine. In many patients the typical symptoms of headache, nausea, and vomiting did not occur in direct association with seizures; and in some patients with migraine alone, symptoms of vomiting, or other portions of the migraine syndrome occurred without headache. In general, although the headaches were reported upon questioning, they were not the most prominent part of the initial complaint in most patients. In 21 cases, or about 40 per cent, the headache was typically temporal and unilateral. In 14, the headache was frontal and temporal and bilateral. In 15 it either was generalized or not explicitly reported with respect to location. In two it was primarily occipital, and in three headache was not a prominent symptom. Only two of the patients had no nausea and vomiting. Of the 55 cases 53 had nausea and 45 had vomiting.

Abdominal pain or discomfort, occurring somewhat more frequently in patients with seizures, was reported in 17 cases or 30 per cent of the total. Twelve of the 33 patients with seizures reported this complaint, whereas only five of the 22 patients with migraine alone complained of abdominal pain or discomfort. There was no particular relationship between this symptom and the findings on the electroencephalogram.

In 20 patients or 36 per cent, some visual disturbance was present at one time or another in association with attacks. Fourteen complained simply of blurred vision, five of a prodrome of glimmering or dancing lights and dots, five of hemianopsia, five of photophobia, one of scotomata, and one of distortion of the shape and size of objects.

Twenty cases reported a denite period of drowsiness or sleep following the migraine attack. In two cases this tendency to go into a deep sleep was the initial complaint which brought the patient to the physician and in one patient, at least, the parent in treating this sleepiness with a patented medicine containing caffeine apparently brought about a marked relief of the migraine syndrome.

Focal changes in the extremities were reported in 18 cases or 33 per cent. These included five cases with numbness alone, three cases with both numbness and jerking, and 10 cases in which there were some jerky movements followed by weakness. Regarding these cases there was considerable difficulty in making a decision as to whether the attacks constituted a convulsive disorder, since in some cases the focal changes occurred at one time by themselves and at another as a prodrome leading to a generalized seizure. When a seizure did not occur such changes were usually associated with or followed by a typical headache.

Other less frequent symptoms included definite pallor associated with attacks, reported by 11 cases; nightmares, and some elevation of temperature, each reported by eight cases; confusion associated with at-

TABLE I

	Alone	With Seizures	Total
SEX:			
Male	10	15	25
Female	12	18	30
AGE:			
Under 3	4	7	11
3-5	8	9	17
6-10	6	12	18
11-15	4	5	9
EEG FINDINGS:			
Normal	7	7	14
Borderline	3	4	7
Abnormal Difuse	8	9	17
EEG Focal	1	10	11
POSITIVE FAMILY HISTORY:			
Of Migraine	15	21	36
Of Epilepsy	2	5	7
MAJOR SYMPTOMS:			
1—HEADACHE	21	31	52
a. Temporal and unilateral	9	12	21
b. Frontotemporal and bilateral	5	9	14
c. Occipital	0	2	2
d. Generalized or no location given	7	8	15
2—NAUSEA	21	32	53
3—VOMITING	17	28	45
4—VISUAL DISTURBANCES	8	12	20
a. Blurred vision	6	8	14
b. Hemianopsia	3	2	5
c. Dancing lights	2	3	5
d. Photophobia	3	2	5
e. Scotoma	0	1	1
f. Shape distortion	0	1	1
5—ABDOMINAL PAIN	5	12	17
6—DROWSINESS	10	10	20
7—FOCAL CHANGES IN EXTREMITIES	5	13	18
Results of Treatment			
CONTROLLED	8	16	24
Barbiturate	6	9	22
Dilantin and Barb.	1	4	1
Other Rx	1	3	1
IMPROVED	10	12	22
Barbiturate	8	6	14
Dilantin and Barb.	1	5	6
Other Rx.	1	1	2
SAME OR WORSE	1	1	2
Barbiturate	1	1	2
Dilantin and Barb.	0	0	0
Other Rx.	0	0	0
NOT FOLLOWED	3	4	7
Barbiturate	2	1	3
Dilantin and Barb.	0	2	2
Rx. Unknown	1	1	2
	22	33	55

tacks, reported by seven; syncope, and some degree of aphasia, each reported six times; enuresis, reported four times, and diarrhea, reported twice.

The results of treatment of these cases are presented in Table 1. In general, the results were very good for control of both seizures and migraine. Control of both was obtained for a period of a year or more in 24 cases or approximately 43 per cent, and another 22 cases were definitely improved, this indicating a control of one or the other type of attacks or a marked reduction in both. Thus, 83 per cent of these cases were either controlled or improved.

Most of the cases were treated with barbiturates and/or some other anticonvulsant drug. The drug treatment given is also indicated in Table 1. One of the major findings of this study is the rather dramatic response of cases with migraine, and with migraine and seizures, at least in children, to continuous medication with rather small doses of anticonvulsant drugs, particularly of the barbiturate family, though in some cases the response was better when drugs of the hydantoin group were added. Barbiturates usually consisted of phenobarbital administered in doses of 16 mg or 32 mg b.i.d. or t.i.d. and Mebaral 32 mg b.i.d. or t.i.d. Dilantin was usually given in doses varying from 32 mg b.i.d. or q.i.d. to 100 mg b.i.d.

Though it is true that the principle of beginning treatment with the barbiturates was followed and thus no good control is available between no treatment, barbiturates, and hydantoin, the fluctuations of symptoms in individual cases when barbiturates were stopped and started has convinced us of the usefulness of these drugs.

Prior to being treated in the Seizure Control Clinic, only a few of these patients had been put on continuous prophylactic medication and the definite response to this was quite striking. The response to continuous medication was much better than that to symptomatic medication of the more specific type such as Ergotamine or Cafergot given at the time of the attacks, though in some cases these preparations were useful in the relief of individual attacks.

Discussion

Migraine and Epilepsy

The first clinician to attempt a correlation of migraine with epilepsy was Tissot[1] who reported observations covering the period 1781-83. He described cases in which he had noted convulsive movements of the facial muscles as well as generalized convulsions associated with migraine. How clearly defined migraine was at that time is uncertain; however, the occurrence of both migraine and epilepsy in the same person later was noted and recorded by Liveing,[2] Hare,[3] and Fere[4] between 1870 and 1890. In Fere's report also had been noted the presence of migraine in the ascendants and descendants of persons subject to the disorder.

Later Wernicke,[5] and in our country, Spratling[6] and Spiller[7] called attention to the relation of migraine and epilepsy. In 1930 Ely reported 171 cases of epilepsy and 15.2 per cent of this group also had migraine.[8] At the same time he also reported a group of 104 cases of migraine in which 8.6 per cent also had epilepsy. In the cases of epilepsy 60.8 per cent reported a history of migraine in their ancestry. Stanley Cobb a few years later in a very extensive review of epilepsy found the occurrence of migraine in the ancestors of a normal control group to be 15 per thousand in contrast to the occurrence of migraine among relatives of patients with epilepsy at the rate of 43 per thousand.[9]

Others, such as Phillips[10] and Gowers[11] had differing opinions; the dissenters, however, have never presented any control studies. Gowers, in 1901, nevertheless reported 90 cases with referred sensations to the head that preceded epileptic seizures. Later Penfield and Kristiansen[12] reported a higher incidence and that many patients complained of headache as a prodromal symptom prior to an attack, with hours or even days intervening between the headache and the subsequent seizure.

Another extensive series was reported by Paskind,[13] who reviewed 3,326 of Patrick's patient records. In this group 783 had epilepsy. The series also included 331 cases without neurological or psychiatric disorders or in the family history. This latter group was considered as a control group. In the group of 783 cases of epilepsy, 35.2 per cent had a history of migraine in the family, 30.8 per cent had a history of migraine in a parent and 8.4 per cent had a history of migraine themselves. Of interest in this connection is Putnam's finding of a 23.3 per cent occurrence of migraine in the 342 cases of trigeminal neuralgia, which must also be considered another related episodic paroxysmal disorder.[14]

Lennox[15] has studied the relationship of migraine and epilepsy extensively and reported that both epilepsy and migraine occurred in 9.2 per cent of a series of 240 patients with seizures. He further reported a greater percentage of positive family history of migraine among the relatives of patients with epilepsy than among the relatives of a control group, and a slightly greater history of epilepsy among relatives of patients with migraine.

Migraine in Children

In recent years Vahlquist,[16,17] Glaser,[18] Krupp and Friedman,[19] Michael and Williams,[20] and Burke and Peters[21] have reported studies of migraine in children. All agree that migraine is more frequent in childhood than is commonly recognized and may have its onset at a very early age. Vahlquist's study of Swedish school children showed an incidence of 4.5 per cent of migraine in children 10 to 12 years old, with 1.9 per cent of these children reporting an onset before the age of six. There is also common agreement that a positive family history of migraine may be obtained in a large percentage of cases, that psychological stress often acts to trigger off attacks, and that abdominal symptoms are more prominent than headache symptoms in children. Also in one or another of these reports reference is made to the associated symptoms of visual disturbance, focal numbness and weakness, syncope, pallor, nightmares, aphasia, etc., which have been recorded in our study.

There is much less agreement, however, as to the importance and frequency of convulsive disorders and electroencephalographic changes associated with migraine in children. This subject is not touched upon

in Vahlquist's reports, and in the 50 cases reported by Krupp and Friedman no associated convulsive disorder was found. On the other hand, five of the 20 cases reported by Michael and Williams had convulsions and of the 14 cases in which an EEG was done, 13 had an abnormal record. Of the 92 cases reported by Burke and Peters, seven had convulsions and of the 67 in which EEG's were obtained, 46 or over two-thirds had abnormal records. It is not suggested in any of these reports that the abnormalities seen in the electroencephalographic record are of any certain type.

Another series of reports[22,23,24,25] concerning abdominal pain in children emphasizes the association with epilepsy and the large percentage of electroencephalographic abnormalities in this condition. Migraine was apparently absent or very infrequent in the cases reported in these studies, though in the original report of Klingman, Langford, Greely, and Hoefer,[22] it was mentioned as occurring in some cases. The same finding of frequent EEG abnormality and associated convulsions is reported by Millichap, Lombroso, and Lennox[26] in 33 cases of cyclic vomiting. All of these cases had some EEG abnormality and nine had experienced convulsions; twelve of these cases, however, had migraine.

Abnormalities in the electroencephalograms of adults with migraine have been reported by Engel, Ferris, and Romano,[27] and by Friedman and Cohn.[28] These reports, and those concerned with abdominal pain and cyclic vomiting in children, at least suggest a relationship of migraine to a primary epileptogenic, and hence neuronal, disorder. A recent report by Bartachi-Rochaix[29] supports the opposite view, that the changes seen in the EEG's of patients with migraine are not specific for an epileptogenic discharge, but rather, are related to a more transitory vasomotor change and are not, therefore, related to epilepsy as such.

Present Study

This study of 55 cases of migraine confirms the findings of others that migraine occurs relatively frequently, and often at an early age, in childhood, that there is usually a family history of migraine, and that psychological factors often trigger attacks. This would indicate that in any episodic condition occurring in childhood, the possibility of a migraine syndrome should be given at least as much consideration in differential diagnosis as a syndrome related to epilepsy. A positive family history, if obtained, is often helpful in supporting this diagnosis, particularly in young children. It has been our experience, however, that direct questioning of the parents and other relatives is often necessary to secure a true history. There are many mothers of patients who are not aware that their husband in his childhood and adolescence suffered from typical migraine attacks. In turn mothers and/or fathers will not often recount their own attacks of migraine suffered in the past, unless specifically asked about it. If the parents' attacks have also been atypical, a reliable history is not likely unless questions are put concerning some of the atypical types of attacks.

It is evident from this study that related to the migraine tendency in children there may be a number of other symptoms which may occur alone or may overshadow the typical headache symptoms. These include either focal or generalized convulsive seizures, severe vomiting attacks, visual disturbances, fever, syncope, confusion, aphasia, nightmares, and focal numbness, jerking, or weakness. All of these symptoms can logically be related to cerebral vascular changes occurring as part of the migraine syndrome. If this is true then the seizures, at least in many cases, are truly secondary in nature and should disappear with the alleviation of the temporary vascular changes. The infrequency of, and the transitory nature of, convulsive symptoms in the present series of cases would suggest that in most instances the convulsive attacks really were secondary to relatively transitory vascular changes and not a manifestation of a more permanent epileptogenic disorder. This notion is further supported by the non-specific changes seen in the electroencephalograms of these patients, among whom only one case was found with a true centrencephalic type of discharge.

This study supports the suggestion previously made that anticonvulsant medication may be very effective in the control of mi-

graine disorders. In more than 80 per cent of our cases, definite improvement was brought about by regular, continuous medication either with a barbiturate, or hydantoin, or both. In a few isolated cases, other medications were effective. There seems to be a hesitancy to put a child upon a regular medication regime of either barbiturates or hydantoin; nevertheless, the severity of the migraine syndrome in many children certainly justifies a trial of this treatment.

The fact that good results may be obtained from anticonvulsive medication is not a definite proof of the essential epileptic nature of the migraine disorder. The effectiveness of phenobarbital in many of our cases indeed suggests a sedative as well as an anticonvulsive effect. It appears from our cases that a decrease in emotional irritability may be a primary factor in the result. Some of our cases without any apparent change in their emotional situation received dramatic effect from medication; other cases did not improve, however, until the emotional and psychological factors were relieved. Our study thus strongly supports the importance of attention to psychological factors as well as to continuous medication. In many cases rather extreme apprehension on the part of the parents over the diagnosis of "epilepsy" was relieved when the diagnosis of "migraine" was made instead, and this change alone was thought to be partly responsible for the improvement of the child.

In this study other drugs of the tranquilizing type were not used, but it is certainly possible that these drugs also used on a long term basis may act as prophylactic measures.

From our study it appears that theoretically at least several situations are possible in the child who reports to a seizure clinic with a tentative clinical diagnosis of both migraine and seizures. First, the condition may simply be one of migraine attacks which due to their severity are mistaken for convulsive seizures. Second, seizures may actually occur, but may often be focal in nature and definitely secondary to vascular changes associated with migraine, and thus being truly secondary are but simply another symptom of the migraine phenomena. Third, migraine attacks and seizure episodes both may be symptoms of the same lesion such as a vascular abnormality, a cicatrix, or a mass lesion occurring in the same person. The occurrence of both migraine and seizures in a few cases reporting head injury, both in our series and that of Burke and Peters suggest this possibility. Fourth, migraine and seizures may occur as two separate and possibly inherited tendencies in the same patient. This is, apparently, the situation in our one case with typical petit mal seizures—such a combination will certainly occur as a matter of coincidence when two conditions are as common in the general population as are both migraine and seizures. It is conceivable, fifth, that seizures may occur as a result of a more permanent neuronal damage brought about by repeated episodes of ischemia due to vasospasm suffered in a migraine attack, or due to thrombosis occurring in a vessel repeatedly subject to spasm. None of the cases in this series represent this picture, but we have seen a few cases among adults wherein apparently a thrombosis has occurred in a patient who has suffered repeated severe migraine attacks for years. Following this the patient has had a focal seizure phenomena, and often the migraine has disappeared. It is possible, finally, that there may be a basic disorder which can occur in individuals and may cause either neuronal or vascular reactions, either appearing together or separately. We have no evidence for this possibility, but it is suggested by the occurrence in some cases of both migraine and seizures in the same family.

Summary

A series of 55 cases of migraine in children seen in the Seizure Control Clinic has been presented. The frequency of this condition in children and its occurrence at an early age have been emphasized. The theoretical consideration of the relationship of seizure states to migraine has been discussed with the general conclusion that severe migraine attacks may be mistaken for seizures in some cases, but that in many cases the convulsive phenomena is actually simply secondary to vascular changes related to migraine.

Excellent results from treatment combin-

ing regular medications with either the barbiturates or hydantoin drug and elimination of psychological stress is reported, improvement or control being obtained in slightly more than 80 per cent of the cases. Prognosis is therefore thought to be good in most such cases despite a severe picture of migraine, seizures and EEG abnormality when the child is first seen.

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A CORRECTION

The Cumulative Index of DISEASES OF THE NERVOUS SYSTEM for 1958 does not correctly list the names of the authors of the article *Ritalin and Serpasil Therapy in Chronic Psychoses, March, pg. 122.* The authors should read Tibor W. Wodraska, John C. Saunders and Nathan S. Kline.

The Unselected Group in Mental Hospitals and Group Treatment of Chronic Schizophrenics

J. W. KLAPMAN, M.D.

Because of prevalent conditions in many mental hospitals outlined in a recently published work,[1] it is very difficult to select patients for group psychotherapy and to maintain the selection once the group has started. In the hurdy-gurdy of the large institution practices there is usually a shortage of personnel and often no one available to bring patients to the sessions nor to escort them back to their wards. The list of group therapy patients the therapist may send to the attendants may not be adhered to, and attendants may send chance selections, chosen by criteria known only to themselves. Group therapy membership becoming thus scrambled a therapist in sheer resignation may decide to do what he can with what he actually receives and to see what happens when the chips are allowed to fall where they will.

In effect, what the therapist then achieves is a group of unselected, mostly chronic schizophrenics. Under such "free wheeling" conditions, it is logical to ask: Can anything be expected? Can any therapeutic results flow from such chaotic circumstances?

Theoretically, it should be possible to proceed with the group of unselected patients in a relatively non-directive and analytic technique. Role-playing, going around by asking each member what his opinion is about his neighbor, or of the institution, or a round in which each member describes the events leading up to his hospitalization, seem to be reasonable entrees. If there are a few better-preserved patients such means may start some interplay, but in a short time, unless the therapist is satisfied with only a two-way communication among one or two patients and the therapist, the action runs down, the patients become silent and inert. Too great a pressure for participation is apt to provoke strong resistance. What seems to be needed with an unselected group of largely withdrawn, unspontaneous, chronic schizophrenic patients is something capable of bringing about general participation, however feeble, in the hope of stirring up more active interest eventually. Such means would have to be a "least common denominator."

This is not to say that intensive, non-directive group psychotherapy can have no scope in a large public hospital. Enough material can be selected from the young, fresh, recently admitted patients in their first or early psychotic breakdown, to keep a number of therapists busy. But what about the others?

Reflections on Psychotherapy Techniques

"A pun is the lowest form of wit," some wag has quipped, and everybody has climbed aboard that bandwagon. Therapists, too, are much concerned with table manners and watch their neighbors closely to see which fork or knife is to be used for each course.

Considering closely that saw about a pun may show that the statement is no interdiction, but merely indicates an order of wit, lesser than some kinds of wit, but not without merit. A penny is the lowest unit in our monetary system, but it still has value. A pun is wit and doesn't merit the obloquy into which it seems to have fallen. Even if we grant that intensive, psychoanalytic group psychotherapy is the highest form of group treatment (which this writer does not) it does not mean that other forms have no merit. But here the analogy ends, for who shall judge of the value of an art which opens the first little chink that permits light to penetrate the darkened prison of the human mind?

Somewhere in his collected papers Freud remarked that this is the method which suits his temperament best, but he had no doubt that another therapist might adopt a different approach. All he specified as psychoanalysis was any method which takes transference and resistance as its start-

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Presented at the Physicians' Association section of the Illinois State Medical Society's Annual meeting, May 1957.

ing point or which takes them into account. Nevertheless, his disciples have set up a more dogmatic system than any he dreamed of.

Corsini[2] in a provocative treatment of this question has strongly suggested that the particular technique of any therapist is practically a direct outgrowth of his personality characteristics. With this there can be little quarrel. What he failed to take note of is that the method of any therapist, although it is the expression of the therapist's personality, is influenced by the indications and the needs of his patients, as the therapist perceives these. In other words, with the conscientious therapist there are some objective determinants of his technique or method of approach to group therapy.

Reflections on Schizophrenia

It appears that there are many roads to schizophrenia. One of the most royal of them is by way of a vacuous mental content. In the absence of orienting concepts, in the absence of a pattern for action which places some reliance on a problem solving approach, the inner life of such individuals is a chaos upon which they float helplessly like corks in the water, without purpose and without reason. The affect may be fundamentally at fault, but whatever the basic pathology, it frequently results in a state of mental vacuity. If through some means order and purposefulness is initiated, that is certainly a structuring or restructuring of the personality, and is genuine psychotherapy in a very real sense.

I have no exact laboratory finding to warrant a speculation about the nature of the up-building process alluded to as psychic integration, except clinical observation. From such observations it does not seem altogether too far-fetched to conceive of psychic functioning in two metabolic phases. There is a phase of anabolism, mostly in childhood when integrations are being built up. Under the most propitious conditions the anabolic phase never ceases, psychic growth process continues prominent to the end, e.g., among sages and seers. Speaking loosely, we may estimate that in the great masses of people the anabolic phase comes to a standstill in the early prime of life with a slow ascendency of psychic ketabolism. In schizophrenia, again speaking figuratively, what appears to be a psychic ketabolism sets in early in life, with a varying speed of ascendency. In many chronic hospitalized schizophrenics this tearing down of integrations appears to be a prominent feature. On the basis of such a postulate the goal and aim of psychotherapy with schizophrenics, especially those of any chronicity, would take a fairly distinct turn.

Again some analogy with physical disease processes seems probable. A disorder may begin with a functional derangement, but in time may come to involve structure. Just so may schizophrenia be considered to involve personality structural changes. With individuals who had perhaps never achieved a serviceable integration and with those in whom the ketabolic process has produced a psychic debacle, analytic psychotherapy does not appear appropriate nor very effective. The techniques of intensive analysis presuppose a quantum which is analyzable, which some of the vacuous states encountered in a great many chronic schizophrenics does not afford. Neither, strictly speaking, does a methodology which can be characterized as synthesis seem appropriate. The needed therapy can be thought of as a stocking-up or restocking of a conceptual matrix for reality-testing, with hope of permitting synthesis in time, which, when far enough advanced, may in the future permit a process of analysis.

The following is a record of the eighth session of a group of schizophrenics who, having been selected and more or less carefully matched, may represent better-preserved, more suitable patients for group psychotherapy. The session is chosen at random from some twenty recorded sessions. The therapist here is psychoanalytically oriented and probably abhors anything which is not nondirective therapy, but notice how, willy-nilly, he is forced to exert even dictatorial direction and discipline. There doesn't appear to be a common ground upon which therapist and patients can meet. These patients do not appear to gain an adequate conception of what the group therapy is about, and it is practically certain in their bewilderment they continue to believe it a waste of time.

Therapist spoke and each patient responded individually. Therapist asked if anyone wanted to be

fed candy. John W. replied: "I would like to be fed a discharge." Howard slapped the table and Bruce blew his whistle. Therapist encouraged both patients to continue with this behavior. Therapist asked, "How do you feel now, Bruce?" Bruce replied, "Like a millionaire." Therapist picked up a piece of candy and gestured to feed Bruce. Howard asked: "Who is keeping us here, a brass or something?" Therapist asked: "Who is keeping you here, Bruce?" "What would you say to someone who could let you out of here, John T.?" John responded "no money" and laughed. Therapist asked Bruce again how he felt. "Do you know what you did then, you stuck your tongue out; what did you do that for?" Therapist continued, "Tom, tell Bruce you don't want your head hit and your ear pulled." Tom replied, "I don't want my head hit and my ear pulled." Therapist said to Howard, "Bruce is getting ready to blow his whistle; he feels that you are talking too much." Therapist directed a question to Sylvester, "Why are you so quiet today?" Sylvester smiled and mumbled something to himself. John W. interrupted and said, "When some of us ask about a discharge shouldn't it be considered serious?" Therapist asked what he was trying to say. John replied, "Well should the question be made a topic for discussion? Why should it be turned over to the class as though their opinion is important?" Howard commented, "I feel like a mother, a mother and father are keeping us here." John continued with his complaints and said, "I don't think my questions should be used for class discussion." Therapist said, "Then you shouldn't bring them up here. You asked to see me privately and I did." John asked if the other people there were audience or doctors. Therapist replied that they were all psychologists. John persisted and said that these things should be discussed privately. Therapist asked, "Since when is your person so sacred that it can't be discussed here? I think that you are bull-shooting me now." John stated that he was angry but in effect he was unable to express it, "I am getting exasperated and I am still mad. I think I have a legitimate self, this is getting rather silly; I am not Bruce, I am more intelligent than any of them." Therapist asked how he felt now. John said: "In what way? I would rather have you answer my question before going into this cross examination." Therapist explained that he was talking about how angry he was. John replied that the therapist had not answered his question. The therapist asked him to repeat it, which John did. "Do you have the right to turn my questions to the group?" Therapist replied, "Absolutely, I have the right." John said that his discharge concerned himself and the doctor. Therapist told him that he was being nasty toward the people he was living with. John said that he thought it was silly to devote so much time to what Bruce was talking about. Therapist cut this off saying, "Why don't we take this up privately; you want the same thing the others want." Tom and Bruce got up and Howard took Tom's seat. John interrupted: "Will you let me talk to the doctor?" At this point Tom, Bruce and Howard walked around the room. John asked if it were true when someone was angry that they dropped their guard. Therapist threw out the question to the group. John stated that he did not want their opinion. Therapist explained that he would not answer any question which could not be considered by the group for discussion. John asked, "Do you want me to answer the group? Can I get a private session with you?" Therapist agreed. Tom became quite angry with Bruce for taking his matches. John directed a question to Howard but received no response. He then directed a question to Sylvester who answered him in agreement. John said, "Now, doctor, will you answer my question?" The therapist replied that he would not. (End of session.)

It seems reasonable that if for any procedure there has as yet not been elaborated special, scientific and uncommon sense, the safest initial approach is to revert to comcon sense. Concededly, it is true that fresh, incipient schizophrenics of suitable personality make-up can be comfortably treated with intensive, analytic, non-directive group therapy, but what about other schizophrenics?

It is to be noted in the above protocol the therapist starts on the assumption of employing actual, analytic, non-directive therapy, but what happens? The therapist is forced to be more dictatorial, arbitrary and even tyrannical than any enlightened directive therapist ever conceived of, e.g., "The therapist replied, 'Absolutely. I have the right!" This is not said to imply inexperience or ineptitude on the part of that therapist. This result must happen if you insist on laying brick with a toothpick instead of a trowel. The approach is wrong.

At several sessions the therapist puts a piece of candy in a patient's mouth. The theory of oral dependency is thereby concretely implemented, and thus a cryptic, mystical, ritualistic practice is inaugurated with very doubtful consequence to the reality-testing capacity of the patient.

"Therapist explained that he was talking about how angry he was," and repeatedly asked how this or that patient feels. He is looking for expressions of hostility on the part of the patients and searching for it so earnestly and persistently that he probably provokes a goodly amount. There seems to be a fairly good theoretical basis for this

attempt to provoke hostility and anxiety. Theoretically, if the patient's hostility is roused for any reason, conceivably, its expression might bring up in its wake some of that deeper, repressed hostility, which then becomes available for analysis. But it is open to question whether that deeply repressed emotion is with any certainty roused by every surface disturbance, provoked by every here-and-now irritation. On a common sense basis such an attempt seems much like Shakespeare's cobbler in "Julius Caesar" who leads the crowd around so that they may wear out their shoes, thus providing him with work. And there are many more indications of the inadequacy of this technique on a common sense basis with this kind of schizophrenic.

Perhaps that is an oversimplification of the conditions, for chronic schizophrenics are to be found in varying states of regression. Not too rarely, one encounters an individual who, notwithstanding signs of severe regression and dilapidation nevertheless retains, back in the interior of the personality, a nidus of sound integration, which can be called forth and expanded. An example of this is a woman, about 50 years of age, from a rather regressed ward, who seemed indistinguishable from her ward mates. After her second group attendance she remains after the other patients have gone and asks a number of mildly anxiety-laden questions, such as "Why can't I go home?" etc. Therapist does not make direct answers but replies with other questions, such as "why are any patients hospitalized. Haltingly and with a little assistance she figures out the answers to these questions. At the end of this exchange she earnestly thanks the therapist and comments how differently she feels about things as a result of the conversation. The essence of this exchange is extremely difficult to reproduce, but the impression that therapist derived was that the sheer intellectual exercise had proved stimulating, the activity of actually reasoning a question through, the novelty of this exercise proved to be an eye opener and stimulating. Surprising as this may seem, if one reflects that this patient has sat on the ward several years, automatically following out unvarying routine orders and rarely in a situation where any genuine problem-solving reasoning was involved, the significance of that exchange can be understood. She achieved an appreciable improvement in her condition as a result of further attendance and her relatives petitioned for her discharge and took her home prematurely, before deriving the maximum benefit from the group therapy.

That woman happened to retain some nidus of sound integration at the core of her personality, which is not easily discovered by the usual tests, but which is more or less readily exposed in group therapy. The reverse of that picture, and unfortunately all too common, is an individual with a repertoire of stereotyped dicta and shopworn adages, giving a semblance of sagacity, but with inner vacuity, devoid of a matrix of conceptions by which reality may be adequately apprehended. One is forced, in many instances, to question which is cause and which is effect. Did the schizophrenia demolish the framework, or was the absence of such a framework of conceptions instrumental in precipitating the schizophrenia? Probably there is ground for either view. This may not be true of all schizophrenics, but it is true of a large number found in the mental hospital.

A mild example which does barely begin to show its important bearing on life adjustment would be the following. In one group session some discussion about memory comes up. It is brought out that one has to think of memory more or less as consisting of two categories, viz., remote and recent. One patient asks what is the meaning of the word, "remote." It is explained. "You mean like going to the commissary or like going downtown?" she asks in some bewilderment. She can appreciate "remote" as signifying physical distance, but the concept of distance in time she seems unable to conceive of. In another instance a patient is talking about her future plans and the difficulties involved. To the therapist the problem is simple, involving persistence at her job and accumulation of a modest sum of money. Desiring to have the patient figure it out he asks a series of problem questions. She cannot answer them. As an objective analogy, reduced to mathematical symbols,

he asks, "if A equals 2 and B equals 4, what would AB equal?" The answer given is 16. Now it may be objected that this is merely a fault in mathematical reasoning, but an eyewitness would have seen that the life problem was juxtaposed on the mathematical one and the patient's failure revealed an absence of a reasonable, logical approach to problem-solving of any kind. It would have been strongly hinted that the patient had little serviceable conceptual framework with which to solve ordinary life situations, and her behavior had consequently been a random, impulsive, acting-out, which I can only conclude brought her into the state of schizophrenia through the numerous frustrations she encountered. A study of the longitudinal life history of this patient seems to bear that out.

A common sense approach to treatment of such a patient is to institute a framework of serviceable concepts on which, if possible, to build a structure of sound adequate reflective thought as the basis for social adjustment. When the personality is sufficiently reintegrated and replete, theoretically it would then be possible to proceed with nondirective analytical treatment.

How does one lay the foundations of that structure? Again a common sense approach is to start from the beginning giving the basic orienting data. As far as I can determine any attempt at this cannot be wholly non-directive and is bound to include a large ingredient of didacticism.

". . . Direct, inspirational group therapy is a dead issue in professional circles," states Bach.[3] Directive it may be, but not necessarily inspirational. Here we encounter the therapeutic taboos.

In groups of 10-15 schizophrenic patients the therapist tries to lead individuals to a consideration of fundamental postulates about the relationship of man to man and to the universe he occupies. In so doing the bases of reasonable and moral behavior must be explored, the why's and wherefore's. From there the specific problems of adjustment of the members of the group will come up for discussion, depending on the degree of articulateness. Even where patients remain silent and inactive, changes in outward behavior often result as Lazell[4] found in his groups. Of course, such considerations are not entirely unknown to the group members. These have been expounded before in school and church, and the individuals have perhaps mouthed them in automaton fashion. Here the path is retraced and attempt is made to reason out the premises and to make them part of the personality. This must involve considerable directiveness and structuring, a degree of enlightened authoritarianism and lecturing—but it is not forced down patients' throats. They have the choice of accepting or rejecting, and in such a group the therapeutic and group dynamics may be observed in incipient form and will be found to have salient differences from that of a purely academic group. Certainly the therapist will be alert to the manner in which the group transactions impinge on each personality and on the group as a whole. His more active participation will show qualitative differences from that of the pedagogue. Of course, there is some overlapping even with the intensest analytical group psychotherapy.

Therapy does not emanate from the mere exposition and imparting of orienting data. If the therapist is to be effective he will have to employ the utmost sincerity. If there is to be a meeting of the minds, the group's and his, in such respects he is most likely to bare the fundamental construction of his own psyche and personality as much as he probes for the comparable structures in his charges. For, if we may again permit ourselves speculation, it is possible to conceive of psychotherapy as a kind of affective osmosis. Moreno, in connection with the dynamics of the psychodrama, voiced the concept of a "matrix of identity." That concept could possibly be expanded to an idea of the "matrix of conceptualizations." The group therapy has the effect, of permitting the patients to absorb some of that matrix from the therapist, while the latter is minutely altered by the exchange. Does this get close to "brain-washing"? It can in the hands of an unscrupulous demagogue.

Patients incorporate part of the therapist's matrix and thus a restructuring is effected. In very few cases is the therapist satisfied that the process has proceeded to its optimum, especially since in large mental

hospital relatives are often apt to withdraw the patient as soon as he shows any signs of improvement. Theoretically, however, a personality may become sufficiently replete and integrated as a result of the therapy to become suitable for the intenser, non-directive analytical forms. In one patient this was observed. The field of group psychotherapy will in time become sensitive to the existence of the many gradations and levels of psychic integration found in patients and will suit the techniques of therapy to the psychic needs of the patients.

If we grant a place for more directive, more didactic techniques in group therapy practices for some patients, a lecture series seems to be the first means to adopt. However, if the lecture series is to have continuity and system, it is well that if he reduced to writing and thus the idea of a textbook comes into being.

The main purpose of a reading text is to serve a stimulus material. While a textbook might be employed effectively with better preserved patients it becomes optimal with many regressed patients who remain silent and inarticulate in group sessions. Powdermaker and Frank[5] have demonstrated how great a problem silence and non-involvement on the part of the patients can be. They give a list of maneuvers which may be adopted to get some patients to vocalize, such as standing behind the patient's chair for an interval, etc. Such maneuvers are not without danger of being misinterpreted by some patients.

If we can overcome our unconscious phobia concerning things academic and pedagogical we may see the value of something that our civilization has caused, very happily, to become as basic (almost as habitual and near-instinctive as walking) as the intellectual exercise and activity of reading. Group reading has been experimented with by Powell.[6] Recently, Kramish[7] has employed group reading in having each member read aloud a prepared letter portraying a different problem. If a more complete airing of diverse facets of reality is desired and if an important desideratum be a methodical building up of a matrix of concepts, then such reading should be well organized and maintain an orderly continuity, as in a book for patients.

Patients read passages of the book aloud and anyone is free to comment. Digressions are followed as long as they have relevancy to the purposes of group psychotherapy. If one little phrase has been read which leads to copious comment and abundant interaction that session is reckoned very productive. Moreover, many other approaches can be combined with the group reading, such as role playing, the "rounds" which Bach speaks of or even the exhibiting of audio-visual material.

Most chronic schizophrenics do not object to reading aloud, and to the extent that they do so and follow the text they become active participants. An atmosphere is thus created which draws from other aspects of the patients' past and is therapeutic, for it draws in a natural way on established institutions—from the atmosphere of a church service or from the schoolroom.

There may be an occasional patient who refuses to read aloud. But even here, however inactive the patient appears to be, some therapeutic influence may nevertheless be exercised. An example is a young woman brought to the group sessions regularly who is not on the list of patients given the ward by the therapist. Because of her inactivity, sitting in a chair all day, she is always available, and the attendant sends her along. Session after session she sits with her head on her chest, not emitting a sound and it seems entirely useless to send her to group therapy. But there came a day when she sat in the front row. Chancing to look at her, therapist observes her head is erect and she smiles with the others over incidental guips in the group proceedings. She refused to come to the group thereafter, although up to that time she had gone along passively as directed. Obviously the refusal of further attendance is due to the resistance which often appears with approaching insight. It was the signal for an individual exploratory interview with her and some earnest solicitation for her continued attendance, but in the hurdy-gurdy of the large mental hospital routines she is lost to view.

Textbook-mediated group therapy may not be the only way of dealing with chronic re-

gressed schizophrenics. It is contended that it may be the method of choice with a large number, and is certainly gentler and more effective than a technique which purports to be non-directive, analytically-oriented and then, because of conditions encountered, turns out to be more dictatorial, possibly more tyrannical than most so-called authoritarian approaches, while uselessly arousing the antagonisms of its subjects.

An experience bears this out and points up indications for textbook-mediated group therapy. Some years ago the therapist was assigned to conduct group therapy with 23 regressed, deteriorated post-lobotomy schizophrenic patients. It was a voyage on an uncharted sea. At the first interview it occurred to the therapist that he would give a brief talk outlining the purposes of the meetings. From there on he would follow "the lay of the land." But that was not to be. No sooner had the therapist begun his talk than a raucous argument broke out between two lozotomees. In another corner a patient began a loud declamation, while here and there one turbulence was about to collide with another and fisticuffs and hair-pulling would be narrowly averted. He would just about have quieted the group sufficiently to start and complete half a sentence when the whole gathering would break out in peals of autistic laughter, usually precipitated by one or two patients. The autistic laughter was the most discouraging drawback. The therapist made another attempt a week later, schooling himself to deliver a simple and understandable talk, for with such a group textbook-mediated group therapy seemed inconceivable. The same situation was repeated and the therapist's eloquence died a-borning; it seemed impossible. However, he was determined to make one more desperate attempt, and if that proved ineffective the project would have to be abandoned. For the third time the therapist brought his textbook titled "Social Adjustment." They were passed around one to each patient and they read sections aloud when invited to do so. In subsequent sessions the loud verbigerations addressed to the air or elsewhere died out; the autistic laughter subsided. From an initially unpromising group of deteriorated appearing patients the group therapy revealed some individuals with residual capacity. Over 25 per cent of these patients improved sufficiently to be discharged.

Summary and Conclusions

1. The more disorganized the personality, the more primitive and archaic the ego, the more directive and structured the group psychotherapy needs to be. Although taken out of context we believe Richmond would concur in the use of his quotation in this connection, to wit: "Just as it would be maladroit to hospitalize, re-educate and serve as guide, model or teacher to a psychoneurotic with a basically reliable ego; so would it be practically gauche to encourage a markedly ego-deficient character to free-associate into a full transference psychosis. It is imperative to evaluate ego function very early in psychotherapy."

2. Wth ego-deficient characters as with regressed schizophrenics it is necessary to rebuild, educate or re-educate the ego, and this requires a more directive, even didactic approach to treatment.

3. We can conceive the directiveness or non-directiveness required by group psychotherapy to be a gradient along whose axis practically any patient can find a point of optimal benefit.

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Neuromuscular Symptoms Simulating Conversion Hysteria Caused by Perphenazine (Trilafon)

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Perphenazine, a tranquilizer in the phenothiazine class, was administered to 560 dermatologic patients, among them a large proportion of psychosomatic cases.[1]

This report is concerned with untoward neuromuscular symptoms which developed in seven of these patients, five females and two males ranging in age from 13 to 22 years, who received perphenazine 8 mg. four times a day, totaling 32 mg. daily.[2]

Symptoms involved the neck, face, eyes, and tongue. In this paper the term "neck-face syndrome" refers to this condition, and "neck-face reactors" to the patients in whom it occurred.

Case Reports

Case 1. A colored female, 15 years old, was hospitalized because of secondary syphilis. From the time of admission she was anxious and depressed, and cried frequently. Therapy consisted of procaine-penicillin, 600,000 units daily, and perphenazine. On the fourth day the patient complained of stiffness of the neck and difficulty in swallowing. Administration of perphenazine was continued despite the complaints. Twenty-four hours later the patient began crying. She said her head felt as if it had been drawn back and that she was short of breath. She was obviously very much disturbed. During examination she was able to move her head freely. There were no objective respiratory signs. Perphenazine was discontinued and the symptoms disappeared. The following day the drug was resumed. The symptoms recurred and the patient was unable to close her mouth because of stiffness of the facial muscles. The symptoms again subsided when the drug was withdrawn. Three days later administration of perphenazine was resumed and the patient was also given 100 mg. secobarbital. The combined treatment was maintained for five days, during which time no untoward reactions occurred.

Case 2. A white female, 22 years old, was hospitalized for a recurrence of acute disseminated lupus erythematosus. She had been hospitalized repeatedly for this condition and had received prednisone, 60 mg. daily, for several months prior to this admission. In addition to prednisone perphenazine was administered in hospital; after 24 hours, the patient complained of stiffness of the neck, trunk, and legs although she could walk without falling. There was a slight protrusion of the tongue which interfered with speaking. The symptoms subsided gradually but several similar episodes occurred within three hours. The patient screamed and moaned. Perphenazine was discontinued and the patient was given 100 mg. secobarbital twice daily. The patient slept after the barbiturate; symptoms disappeared and did not recur.

Case 3. A colored female, 13 years old, was hospitalized for generalized pyoderma and pruritus. She received procaine-penicillin, 600,000 units daily, and perphenazine. The course was uneventful until the fourteenth day of therapy, when the patient began to scream. Her head was thrown back and there was stiffness of the neck. The eyes were rolled back and staring, and the face and mouth twitched. Perphenazine was discontinued and the patient was given secobarbital, after which she slept for two hours. She then left her bed and another seizure occurred within 10 minutes. Barbiturates were again administered and no further reactions occurred.

Case 4. A colored male, 14 years old, was hospitalized for pruritic linear scleroderma of the upper extremities. Perphenazine was given. After the third dose the patient experienced stiffness of the neck and shoulder, and tremor of the hands. The drug was discontinued.

Neurologists and psychiatrists were called for consultation in each of these cases. Examination immediately after the seizures revealed normal cranial nerves, pupils, fundi, and motor and sensory systems. Electroencephalographic examinations were performed in two of the four patients before administration of perphenazine and after symptoms subsided; no changes were observed. The possibility that perphenazine may have provoked attacks in our patients was considered unlikely since the syndrome had not been observed previously. As the number of cases increased a diagnosis of group hysteria was made, based on the similarity of symptoms in all four patients and the fact that

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all episodes occurred in the same room of the ward within one week.

In order to distinguish between psychologic and pharmacologic factors, Patient 4 was given 8 mg. perphenazine in disguised form. One hour later, he experienced a typical seizure: the head was drawn back, the eyes rolled, the mouth was open and the patient moaned. Several intermittent attacks of the same type, although of diminished intensity, occurred within four hours. Perphenazine was discontinued for four days, during which time the patient felt well except mild discomfort in the neck. He was then given placebos for two days and remained free from symptoms. Perphenazine, again in disguised form, was then resumed. A seizure occurred after the fourth dose and there were several attacks until secobarbital was given, at which time symptoms quickly disappeared. It was therefore concluded that the neck-face syndrome was caused by perphenazine and was not a manifestation of group hysteria.

Case 5. A colored male, 15 years old, was hospitalized for atopic dermatitis. On the third day of treatment with perphenazine he developed stiffness of the neck. Aspirin, 10 gr., brought relief within one hour. When perphenazine was resumed, the attacks recurred and were relieved by 100 mg. codeine. Cases 5 suggests that the effect of barbiturates in relieving the face-neck syndrome was not specific.

Case 6. A colored female, 20 years old, was hospitalized for urticaria. On the second day of treatment with perphenazine she experienced stiffness of the neck, for which she was given a hot water bottle; perphenazine was discontinued for the day. The next day it was resumed but the dosage was halved. The patient has been maintained on 16 mg. daily for two months and there have been no further undesirable reactions.

Case 7. A white female, 20 years old, was hospitalized because of atopic dermatitis. On the ninth day of treatment with perphenazine she developed facial symptoms but no other neuromuscular manifestations. She was not greatly disturbed. Perphenazine was maintained but the dosage was reduced to 12 mg. daily for five weeks and then 16 mg. daily for two months. No further reactions occurred.

The neck-face reactors were observed during the attacks and interviewed several times after the attacks subsided.

Comment

Neuromuscular reactions during treatment with chlorpromazine-reserpine and prochlorperazine were previously reported by other authors.[3,4,5,6,7,8,9*] In our observations the neck-face syndrome in the seven cases reported above assumed the following pattern: Immediately before each attack the patient experienced a feeling of uneasiness and a desire to lie down and stare. The neck then became stiff and the head was fixed forward, backward or laterally. The patient supported his head with his hands, "as if he attempted to prevent the head from falling." He was unable to close the mouth. The tongue protruded and appeared broadened, rounded, and arched; it could not be retracted or pushed into the mouth manually. Salivation increased notably. Patients were fully conscious during seizures and experienced pain only on attempts to move against the contracted muscles.

These symptoms occurred singly or in combination. The tonic seizures, each lasting five to 12 minutes, recurred at intervals of 10 to 30 minutes. Unless treated for the seizures the patients experienced three to six attacks in a series; the duration and intensity of each succeeding attack diminished gradually. The time interval between the start of perphenazine therapy and occurrence of the first seizure varied from 12 hours to 14 days. The interval between the last dose of perphenazine and the occurrence of the attack varied from one to 12 hours. The patients showed great anxiety during the seizures and often screamed, cried, or moaned. The attacks resembled hysteria to such an extent that the diagnosis of drug reaction was thought highly unlikely until it was confirmed.

Attacks in these patients recurred when perphenazine was resumed at the original level of 32 mg. daily; however, when dosage was reduced they tolerated continued administration for several months without untoward reaction.

Seizures recurred rapidly in the patient who left her bed immediately upon awakening from the short sleep induced by secobarbital. This suggests to us that neck-face reactors should be kept in bed considerably

*(8 & 9) Appreciation is due to Fritz A. Freyhan, M.D., for drawing our attention to previous reports on similar reactions with other phenothiazine compounds.

longer than 4 hours even if they were relieved by barbiturates. Barbiturates. Barbiturates appear to reduce the number and intensity of seizures in a series and may even, as in Patient 1, prevent attacks during administration of perphenazine. Further study among a large group of patients is needed to confirm this assumption.

Four of these patients received perphenazine alone, two received perphenazine and procaine-penicillin, and one received perphenazine and prednisone. We can therefore conclude that the seizures were not due to enhanced toxicity of penicillin or prednisone induced by perphenazine and that neither of the former drugs played any part in provoking the attacks.

Perphenazine should be adminitered only under careful medical supervision and dosage must be adjusted individually in each case. The initial dose, which should be low, can be increased gradually until the desired effect is obtained. Thereafter patients should be maintained on the lowest effective dose.

In psychosomatic dermatoses dosage should be initiated at 8 mg. daily in adults and 4 mg. daily in children, in divided doses. Rarely, if ever, should it exceed 16 mg. daily in adults or 8 mg. daily in children. When higher initial doses are required in young, very tense patients, the simultaneous administration of barbiturate, codein, or aspirin may afford protection against untoward reactions. We also suggest that perphenazine be administered together with barbiturates at the beginning of psychotherapy when tension is high; later, the barbiturates can be withdrawn as the dosage of perphenazine is reduced.

Summary and Conclusions

A neck-face syndrome simulating hysteria causedd by perphenazine is described. It occurred in seven patients with psychosomatic dermatoses who were treated with 32 mg. perphenazine daily. The episodes appeared as a series of tonic seizures involving the neck, face, eyes, andd tongue. The seizures lasted five to 10 minutes and recurred, diminished in intensity and duration, at intervals of 10 to 30 minutes. Barbiturates, aspirin, or codeine relieved the neck-face symptoms.

These seizures occurred when dosage exceeded 16 mg. daily. When higher dosages are essential, barbiturates may prevent the occurrence of the untoward reactions.

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Evaluation of Two Ataractic Agents

Experience of One Year with Prochlorperazine and of Seven Months with Benactyzine

N. WILLIAM WINKELMAN, JR., M.D.

As the number of drugs that influence mood, affect, and behavior increases, it becomes more and more important to conduct a careful investigation of each so that no therapeutic advances go undiscovered. For example, the investigation of such a drug may reveal that it is specific for treating particular psychiatric entities; that it is effective where similar drugs have failed; that it has a lower toxicity; that it has a more rapid or prolonged effect; or that it possesses a mode of action entirely different from that of the drugs currently in use.

With these possibilities in view, an investigation of two drugs was undertaken. One of the compounds studied was the phenothiazine derivative, prochlorperazine (Compazine*). The structural similarities of this drug to chlorpromazine gave promise of similar pharmacologic activity, but the dissimilarities suggested that prochlorperazine might offer benefits different from those of the parent congener. This hypothesis was based on pharmacologic studies of prochlorperazine which revealed pharmacodynamic properties similar to those of chlorpromazine, but which suggested that prochlorperazine had more potent therapeutic activity, and that it was less toxic. Earlier studies[1,2] of chlorpromazine in a similar patient group provided a background of experience for the present evaluation.

The other drug investigated was the benzilic acid derivative—benactyzine hydrochloride (Suavitil†), an anticholinergic that is believed to produce tranquilization through its effects on the basal ganglia and such functions as perception of movement and maintenance of muscle tone. Preliminary reports by Danish and British investigators[3,4,5] indicate that this compound was effective in patients of the type selected for trial of prochlorperazine.

Method

I. Prochlorperazine

Two hundred and seven outpatients were treated with prochlorperazine. This series included 188 psychoneurotics of various types, 186 of whom displayed an anxiety reaction as part of their clinical syndrome, and 19 schizophrenics with delusional reactions; seven of the 19 patients also exhibited depressive reactions. The individual reactions comprising each patient's clinical syndrome are shown in Table II. Fifty-six patients, all of whom had responded well to chlorpromazine, reserpine, or meprobamate, were included in this study after a drug-free period to eliminate carry over effects. The preliminary evaluation of each patient included diagnosis, psychodynamics, and prognosis. Psychological tests, where indicated, were given.

Patients were started on one 5 mg. tablet of prochlorperazine three times a day. Each patient's daily dose was increased by small increments until the optimum therapeutic dosage was established. Patients were seen at weekly intervals during the first two months, and bi-weekly thereafter. Re-evaluation of the patients' symptomatology and, if necessary, adjustments in dosage were made during each visit.

During the last four months of this study, prochlorperazine was made available in 15 mg. sustained release (Spansule) capsules which provided therapeutic effects for 12 hours. These capsules were prescribed for 15 patients, once or twice daily, depending upon the patient's need for therapeutic effect during the evening and night.

The 207 patients were studied for periods ranging from four to 12 months; more than half of them were studied for eight months or longer.

*T.M. for 2-chloro-10-[3-(1-methyl-4-piperazinyl)-propyl]-phenothiazine; Smith, Kline & French Laboratories.

†T.M. for 2-diethylaminoethyl benzilate hydrochloride, Sharp & Dohme Laboratories.

II. Benactyzine

Sixty psychoneurotic patients were treated with benactyzine. Except for two "borderline schizophrenics," these 60 patients were similar to the prochlorperazine-treated psychoneurotic patients in their individual reactions (Table III), and in their intellectual, social, and economic backgrounds. Benactyzine dosage was built upward in small increments from 1 mg. three times a day, in an attempt to establish optimum therapeutic doses. Although this study was continued for seven months, none of the patients received the drug for longer than four months; half of the patients were studied for less than four months.

Results for patients treated with both drugs were based on improvement in individual reactions and, to avoid false positive results (spontaneous changes or substitutions in individual reactions), improvement in the overall syndrome. Marked improvement indicated 75% or more improvement; moderate improvement, 50 to 75%; slight improvement, 25 to 50%; no improvement, 25% or less.

Results

I. Prochlorperazine

Among the patients treated with prochlorperazine, marked improvement in the overall syndrome was shown by 91 (44%), moderate by 74 (36%), slight by 26 (12%), and no improvement by 16 (8%). The psychoneurotics, as a group, responded better than the schizophrenics (Table I).

Among the individual psychoneurotic reactions, anxiety responded best (Table II). Improvement was marked in nearly half of these reactions, and moderate in most of the others. Marked or moderate improvement was shown in well over half of the conversion reactions and the phobic reactions, and in nearly half of the obsessive reactions. Depressive reactions associated with anxiety responded very well; those not associated with anxiety responded slightly. It should be noted that prochlorperazine did not increase depressive reactions in any of the patients.

Among the individual schizophrenic reactions, marked or moderate improvement was shown in more than half of the delu-

RESPONSE TO PROCHLORPERAZINE

TABLE I—CLINICAL SYNDROMES

Diagnosis	No. of Patients	IMPROVEMENT			
		Marked	Moderate	Slight	None
Psychoneurosis	188	86 (46%)	68 (36%)	19 (10%)	15 (8%)
Schizophrenia	19	5 (26%)	6 (32%)	7 (37%)	1 (5%)
Totals	207	91 (44%)	74 (36%)	26 (12%)	16 (8%)

TABLE II—INDIVIDUAL REACTIONS

A. PSYCHONEUROTIC REACTIONS*

Reaction	No. of Cases	IMPROVEMENT			
		Marked	Moderate	Slight	None
Anxiety	186	92 (49%)	82 (44%)	8 (4%)	4 (2%)
Conversion	52	11 (21%)	23 (44%)	13 (25%)	5 (10%)
Phobic	25	5 (20%)	14 (56%)	4 (16%)	2 (8%)
Obsessive	12	1 (6%)	5 (42%)	2 (17%)	4 (33%)
Depressive	23	2 (9%)	16 (70%)	5 (21%)	0 (—)

B. SCHIZOPHRENIC REACTIONS

Delusional	19	5 (26%)	6 (32%)	7 (37%)	1 (5%)
Depressive	7	0 (—)	0 (—)	0 (—)	7 (100%)
	26				

*Some patients exhibited more than one reaction.

sions (Table II). The depressive reactions showed no significant improvement; in fact, the drug seemed to reinforce depression in these patients.

The 56 patients who had been treated previously with meprobamate, reserpine, or other phenothiazines, reported the absence of abnormal psychological effects during the onset of prochlorperazine's actions. Thirty-one of these patients showed a better therapeutic response to prochlorperazine, and 15 responded as well to prochlorperazine as to their former medication.

Optimum therapeutic dose for most patients was between 20 mg. and 50 mg. daily, although extremes ranged as low as 5 mg. and as high as 80 mg. daily. Like other phenothiazine derivatives, prochlorperazine requires highly individualized administration. Patients taking the sustained-release capsules reported that the effects of an evening dose usually persisted until the next morning. In 35 of the 207 patients, dosage had to be increased after the optimum dose apparently had been achieved, as they seemed to develop partial tolerance to the drug. Doses were administered at shorter intervals in these patients.

The only side effects observed with prochlorperazine were drowsiness, undesirable weight gain, and transient agitation. Mild, transient drowsiness was seen initially in 49 patients; disturbing drowsiness was seen in 23, but most of these patients developed tolerance to it. If tolerance did not develop quickly, the drowsiness was successfully overcome by a 2.5 mg. tablet of dextro-amphetamine sulfate with doses of prochlorperazine during waking hours. Weight gain of more than 5% was seen in 38 patients, but was a desirable effect in 30 of these patients. A paradoxical state of agitation was produced in two patients as their dosage was being increased, but disappeared on continued medication.

II. Benactyzine

Slight or moderate improvement was observed in 15 (25%) of the 60 patients treated with benactyzine. Thirty-seven (62%) were unchanged, and eight (13%) became worse while taking the drug. None of the individual psychoneurotic reactions treated with benactyzine showed marked improvement (Table III).

Benactyzine produced a disruptive side effect, severe absent-mindedness, which caused 20 of the 60 patients to stop the drug voluntarily. Nearly all of the other patients complained of this effect, even before the optimum therapeutic dosage had been established. After their daily dose was raised above 6 mg., these patients had transient moments of disorientation. This effect did not disappear on continued medication, and it reappeared after temporary withdrawal and reinstitution of the drug.

The two borderline schizophrenics given benactyzine developed a severe problem in distinguishing the real from the unreal. The drug was stopped and re-started several times, but each time both patients suffered frightening unreal feelings that permeated their entire environment.

The final dose level for most of the patients was 6 mg. per day, given in three 2 mg. doses. Some of the refractory cases were given as high as 12 mg. per day without significant benefit.

RESPONSE TO BENACTYZINE

TABLE III—Individual Reactions*

Reaction	No. of Cases	Improvement: Marked	Moderate	Slight	None
Anxiety	33	0 (—)	3 (9%)	8 (24%)	22 (67%)
Phobic	6	0 (—)	2 (33%)	2 (33%)	2 (33%)
Obsessive	10	0 (—)	2 (20%)	3 (30%)	5 (50%)
Depressive	11	0 (—)	5 (45%)	3 (27%)	3 (27%)
	60				

*Only the predominant reaction was evaluated.

Comment

In comparison with other compounds with similar therapeutic effects, prochlorperazine exerts its pharmacologic actions very smoothly. Both the onset and the course of its action left the majority of patients relatively unaware of drug effects. This effect is important for all patients, but especially for those with a tendency to hypochondria, since such patients may develop a negative psychological reaction that will cause them to resist, or even stop, taking a drug. Improvement of sleep patterns was reported by most of the patients receiving prochlorperazine. None of the usual complaints of vague or bizarre subjective response to drug action was reported. In many patients, this drug provided dramatic relief of worry. In a few patients, however, the drug seemed to reduce motivation and induce complacency.

Prochlorperazine's chief characteristic is its combination of high effectiveness with low toxicity. The actual therapeutic value of this drug is high in both psychoneurotics and schizophrenics with anxiety reactions and syndromes which include a large element of anxiety; it is also very effective in other reactions. Prochlorperazine does not exacerbate psychoneurotic depression; in fact, depressive reactions respond well to it, especially when they are associated with anxiety.

Prochlorperazine's low toxicity makes it as safe as any available tranquilizing drug for use in psychoneurotic and schizophrenic outpatients. Since side effects present no serious problems with prochlorperazine, dosage may be readily increased, and the drug may be administered in long-term therapy.

Benactyzine was found to be generally ineffective in psychoneurotics. Despite its benefit in some depressive reaction, benactyzine is of very little benefit in anxiety or obsessive reactions. In general, its actual therapeutic value seems low.

Severe absent-mindedness, which caused one-third of the patients to stop benactyzine, outweighed the benefits of the drug in another one-third of the patients. The appearance of frightening unreal feelings in the borderline schizophrenics when the drug was re-started makes the author wonder whether this drug could not be used as a test for this common and often difficult to recognize entity. The reactions would also suggest that the drug is contraindicated in schizophrenics with a problem in the sense of reality or any disassociation problem.

Summary

Two drugs—prochlorperazine and benactyzine—were evaluated in separate but similar groups of patients.

Of 188 psychoneurotics and 19 schizophrenics treated with prochlorperazine, 80% showed marked or moderate improvement in their clinical syndromes. The psychoneurotic reactions, especially anxiety, responded very well to prochlorperazine, as did paranoid delusions in the schizophrenics. The patients were free of disturbing negative psychological effects while on the medication, and their ability to sleep was significantly improved. Prochlorperazine provided no serious or prolonged side effects during one year of administration.

Of 60 psychoneurotics treated with benactyzine, 25% showed slight to moderate improvement in their clinical syndromes; the syndromes of remaining patients either remained unchanged or became worse. Severe absent-mindedness disrupted therapy in 40 patients, causing 20 of them to stop the medication voluntarily.

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Treatment of Depressed and Regressed Patients with Iproniazid and Reserpine

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Some 5 years ago the newspapers were filled with accounts of a new drug for the treatment of tuberculosis. There were pictures of patients dancing in the wards as a result of this medication. Subsequent studies revealed that although the drug, iproniazid, was therapeutically active, investigator after investigator commented upon the fact that "the degree of symptomatic improvement almost invariably exceeded the degree of radiological clearance,"[1] or "symptomatic response was frequently out of all proportion to objective improvement as determined by roentgenographic or bacteriologic studies."[2] There was unanimous agreement that the patients showed a remarkable sense of well being, had ravenous appetites, and showed marked and rapid weight gains. Upon more prolonged usage it was found that iproniazid brought with it certain severe side effects in a fair proportion of the cases treated. In the second paper just referred to, the authors found that 6 of 44 patients developed psychoses. In another publication 23 of the 142 tuberculous patients showed some psychic change with 11 developing a psychosis. The most interesting comment was by Bosworth[3] who noted that when the psychoses are described it is stated, "These were generally of euphoric type."

In the psychological area the concentration was so intense upon the side effects that the possibility of therapeutic application to psychiatric patients was generally overlooked. In the search for agents with which to modify schizophrenia (and this was before the "tranquilizer era") three studies were done on schizophrenic patients. One of these concentrated almost entirely upon the seizure-producing capacity of the drug;[4] another was a short-term across-the-board study of a variety of psychiatric conditions,[5] and the third was on the behavior of long-term mental patients.[6] These studies concluded that the drug had no practical significance in the field of psychiatry.

In the meantime pharmacologists and neurochemists, in their effort to elucidate the enzyme systems involved in cerebral metabolism, had utilized iproniazid[7] and other amine oxidase inhibitors as investigational tools. When the efficacy of reserpine in both hypertensive and psychiatric conditions was demonstrated, iproniazid began to play a role in many of the laboratory studies. It had been found that if an animal had first received iproniazid and was then given reserpine, instead of the expected sedation occurring the animal tended to exhibit increased activity and excitement. Curiously enough, if reserpine was administered first, iproniazid did not produce this effect.[8,9]

Because of our own interest in the use of reserpine in psychiatry we were continually looking for assistance in clarifying the mode of action of reserpine. One of the great gaps in pharmacotherapeutic handling of psychiatric patients is the lack of adequate medication for the deeply depressed and regressed patient. A possibility occurred to us that the iproniazid and/or reserpine regime might be of value for this purpose since it certainly "stirred up" the experimental animals.

There were theoretical considerations which led us to believe that this might be a rational approach because of the ability of iproniazid to inhibit amine oxidase in the metabolism of epinephrine, nor-epinephrine, tryptophane glutamine, histamine and possibly other amines. It is possible that the "euphoria" reported in tuberculous patients is associated with this reduction in oxidative deamination and to an increase in the methylation of nor-epinephrine to epinephrine and other essential amines. Fragmentary data at this time indicate the methyla-

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Data and opinions are as of the time of presentation at the Society for Biological Psychiatry, Atlantic City, N. J., June 1957, only a month after the first paper describing its use for depressed and regressed patients.

tion of serotonin to bufotenin is increased two-fold when iproniazid is given. One of the balancing factors between these two groups of amines is transmethylation.

One of the clinical side effects of iproniazid administration may be a deficiency in pyridoxine (Vitamin B_6). Glutamic acid decarboxylase is sensitive to a carbonyl reagent such as semicarbazide and requires pyridoxine as a coenzyme; therefore, one would speculate that iproniazid having a carbonyl group could easily interfere with this enzyme system. The influence of dietary pyridoxine on glutamic decarboxylase in the brain of rats has been investigated by Roberts *et al.*[10] and they report a decrease in the initial rate to about 50% of the control value. The alpha-decarboxylation of glutamic acid forms gamma-aminobutyric acid and this compound is found in relatively large amounts in the brain of many animals including man. It is of marked interest that the gamma-aminobutyric acid-glutamic decarboxylase system is highly concentrated in the gray matter of the central nervous system.[11] This could lead one to believe that its function is important to conduction of nerve impulses and may actually act as a stimulant by depressing inhibitory areas as indicated by changes in polarization of the dendritic processes.

It has been established that 5-hyroxyindole compounds were derived from the amino acid tryptophane and some of the processes were elucidated for the production of serotonin. The demonstration of serotonin in the central nervous system by Amin *et al.*[12] and the neurophysiological and pharmacological aspects of serotonin led Wooley and Shaw[13] to propose that interference with serotonin metabolism might be the cause of certain types of mental illness. The administration of parenteral serotonin has produced few central nervous system responses, although several peripheral symptoms were reproduced. Bogdanski *et al.*[14] found a rise in serotonin levels in the brain after the administration of 5-hydroxytryptophane which led to the assumption of specific central nervous system decarboxylase for 5-hydroxytryptophane. Serotonin levels increase after iproniazid administration which would indicate that it is without effect on the decarboxylase essential for serotonin production and a specific decarboxylase is present as previously suggested. However, it is difficult to accept the conclusion of Sjoerdsma *et al.*[15] that the toxic effects of iproniazid are due to its prolongation of action of serotonin since the symptomatology is not comparable to that associated with malignant carcinoid with its high serotonin level.

It has been observed by Elmadjian[16] that aggressive-hostile patients had increased excretion of nor-epinephrine and passive-fearful ones had increased excretion of epinephrine. Garb *et al.*[17] recently introduced the concept that depression may be the result of approximately equal quantities of "hostility and anxiety producing" amines. Iproniazid is a very potent pharmacological determinant in regulating the enzymatic systems responsible for oxidative deamination of essential amines. Amine oxidase is conceded to be responsible for about 50 per cent of the degradation of epinephrine and Teague and Wingard[18] indicate that these aldehydes may have sympathomimetic properties. Schayer[19a,b] postulated there are at least two pathways in the breakdown of epinephrine; however, the possibility of a phenolase enzyme system exists. Also, Werle[20] observed that epinephrine inhibits 1-histidine decarboxylase and this suggests epinephrine may block the formation of histamine. The role of histamine as a neurochemical mediator is still unknown but deserves attention since Zwiatkowski[21] reaffirmed the presence of histamine in mixed somatic nerves and found a particularly high concentration in dorsal root fibres.

These observations indicate that iproniazid has both a direct and indirect action on the balance of a number of amines essential for normal neurochemical activity. The direct action is as an amine oxidase inhibitor. The indirect action is associated with transmethylation and pyridoxal decarboxylase and the latter's function in the formation of epinephrine, nor-epinephrine and histamine due to the exchange reaction between the nicotinamide moiety of disphosphopyridine nucleotide and related compounds such as iproniazid.[22a,b]

Our clinical observations with iproniazid are that its action is primarily on the cen-

tral nervous system. It has been reported by Bosworth *et al.*[23] that spinal fluid levels have an average increase of 58.1% above those found in sera. Iproniazid sera levels in 10 patients sampled once weekly, beginning at the 5th month of therapy, for a 5-week period average 0.15 mg. per cent.[24] Peripheral edema and skin rash were seen in one patient with a 0.57 mg. per cent concentration in the sera.

Inhibition was obtained in vivo studies[25] against acetylcholine bromide cholinesterase on patients receiving iproniazid. The changes observed were not significant when compared to the controls; however, Scherbel[26] has reported a significant drop in cholinesterase sera levels in patients that demonstrated effects such as hyperreflexia and clonus.

Subjects

A. We therefore selected depressed withdrawn patients regardless of diagnostic category. In contrast to the hyperactive, agitated, assaultive patients in whom reserpine and the phenothiazine derivatives act most effectively, the patients in this study were uniformly colorless personalities of the chronic so-called "burned-out" psychotic variety. Baseline studies on the 21 patients selected made it necessary to eliminate 3 (2 because their psychomotor activity showed fluctuation which might be misinterpreted as improvement and 1 because of possible renal pathology for which iproniazid may be contraindicated). This study, therefore, consisted of 18 long-term stabilized patients who had shown virtually no evidence of interest in their surroundings for a number of years and most of whom appeared withdrawn and depressed (with no evidence of agitation). These results have already been presented.[27]

B. Thirty patients, not only of the idle, withdrawn, or depressed type but also agitated disturbed types were selected for treatment with the iproniazid-reserpine combination. Half were given iproniazid for one week (50 mg. t.i.d.) and then had reserpine (1.0 mg daily) added. In the animal experiments, if reserpine was given first, the response did not occur. Therefore, the other 15 patients were started with a week of reserpine to which the iproniazid was then added.

C. Fourteen among almost 50 patients of which we know who have been treated in private practice (ap. 1, 2, 3, 4, 5) are also included. These patients were selected also on the basis of showing symptoms of withdrawal or depression. Diagnostic categories, age, and other characteristics are described individually along with the course of previous treatments under the case histories.

Setting

A & B. The chronic institutionalized patients were treated on the usual wards in an 8,000-bed state hospital in which they had been residents for an extended period and were not transferred to the research ward. Evaluations were done by the ward psychiatrists and were based on their clinical impressions plus those of the nursing and attendant staff. Since almost all of these patients had received one or more courses of other medications, it is unlikely that simply receiving a tablet, per se, could have resulted in improvement since this would otherwise have occurred in one of the previous courses of drug administration. The patients are housed in buildings which contain approximately 600 patients which is ordinarily serviced by one psychiatrist and the wards on which they were situated house approximately 70 comparable patients.

C. The patients reported from private practice were seen in the physician's office and, except as noted, were treated from one to three times a week for the customary hour. Most of the patients had received previous treatment including a variety of pharmaceuticals without satisfactory response. Some of the patients had been in treatment with their present therapists for more than a year.

Experimental Design

As this was a pilot experiment no attempt was made to use double blind or placebo techniques. The utilization of elaborate format is pointless until there is some evidence that the medication is active and until dosage range has been determined.

In most cases both the patients and the psychiatrist were familiar with drug usage and there existed no greater enthusiasm as

to potentialities of this treatment than with numerous other medications. Since among the hospitalized group only well stabilized subjects were chosen, the patients could truly be said to have acted as their own controls.

The plan of investigation, based on the animal experiments, called for the "pretreatment" of patients with iproniazid which was to be followed by the administration of reserpine. It was obviously also necessary to determine the effect of iproniazid alone since if reserpine were added before the effects of the first drug could be evaluated, it would be impossible to determine whether any beneficial results were due to the iproniazid or to the combination of iproniazid and reserpine. It was also important to check if the prior administration of reserpine reduced the effectiveness of the iproniazid as in the animal work. It was the original intent to use only iproniazid in the "A" group but, as seems to inevitably be the case, two of the group have been deviated insofar as reserpine (1 mg. t.i.d.) was added to one regime and a second patient had been on 1 mg. of reserpine and 50 mgs. of chlorpromazine t.i.d. for several weeks prior to starting iproniazid and was continued on this same regime.

Dosage and Duration

The critical dose at which side effects usually manifested themselves in the treatment of tuberculosis patients was 300 mgs. a day. Ideally one would look for therapeutic efficacy at a dosage low enough to circumvent the occurrence of undesirable side reactions. We, therefore, arbitrarily took half of this dose and started all patients on 50 mgs. of iproniazid t.i.d. In one of the hospitalized patients the dosage was raised to 75 mgs. t.i.d. without any side effects, but in a private patient who was given a total dosage of 250 mgs. a day it was necessary to return to the original 150 mgs. because of dizziness. In another of the private patients the same feeling of dizziness necessitated reducing the dosage to 25 mgs. t.i.d. After a short time on this dosage the patient was returned to 50 mgs. t.i.d., but the dizziness again recurred and dosage was again returned to half that amount. If the patient refuses oral iproniazid we had given 25 mgs. i.m. daily until cooperation was obtained. In patients with hypertension, initial dose should be low since a precipitous drop in blood pressure (for any reason) is dangerous. Severe postural hypotension can be handled with 12.5 mg. of cortisone b.i.d. If edema occurs a diuretic is usually adequate. Incidentally, weight gain is accompanied by positive nitrogen balance so it is *not* due to edema in the usual case.

It is very strongly recommended that doses no higher than 150 mgs. a day be given in view of the probability of side effects. These, except dizziness, mild constipation, delayed micturition, edema, and delay in onset of sleep were not usually found on the dosages used here. On higher doses in tuberculous patients there are also reports (in order of troublesomeness and frequency) of hypotension, twitching of lower extremities, ataxia, hyper-reflexia, drowsiness, dryness of mouth. Also rarely reported (on very high dosages) as possibly drug related are: peripheral neuropathy, impotence, jaundice, palpitations and euphoric psychoses. Therefore, the need to individualize therapy is essential with iproniazid as with all drugs.

Dr. Speigel made the observation that by adding 5 mgs. of d-amphetamine* once or twice a day to the iproniazid that in many patients the response can be remarkably accelerated. Therefore, for a rapid response the patient should be placed on 50 mgs. of iproniazid t.i.d. and 5 mgs. of d-amphetamine either in the morning or in the morning and at noon. Doses later in the day tend to induce insomnia in some of the patients although Dr. Sandler has found that iproniazid alone has led to improved sleep in other patients. This regimen should be continued for three to five weeks unless a satisfactory response is obtained sooner. If sufficient improvement has not been obtained at the end of that time 1 mg. of reserpine a day should be added to the other medications and continued for another 2 months before therapy can be regarded as having been ineffectual.

*The d-amphetamine used in this study was supplied by Smith, Kline and French Laboratories, Philadelphia, Pennsylvania, under the name of Dexedrine.

If satisfactory response is obtained and has been maintained for approximately one week, the dosage should then be reduced. At the present time and until further evidence is available it is not recommended that patients be kept on a maintenance dose of iproniazid. If maintenance is necessary because of return of symptoms upon withdrawal, it must be individualized and can range anywhere from 10 mgs. twice a week to the full 50 mgs. t.i.d. Since the drug is a cumulative one, action tends to be prolonged for a considerable period after its withdrawal. This should be taken into account in regulating the dosage. The other important point in respect to accumulation is that if the drug is continued long enough on even moderate doses there may be a tendency for side effects to develop and it is therefore recommended that as low a maintenance dose as possible be utilized. This can usually be determined by gradual reduction of dosage at the rate of perhaps 25 mgs. a week and continued downward unless there is evidence of recurrence of symptoms. We have thus far used a minimum of 10 mgs. per day in those patients whom we intend to maintain on the drug.

Results

A. Although the first patients tested were in the "B" group the first results to be presented were those on patients treated with iproniazid alone. This paper by Loomer, Saunders and Kline was delivered at the Regional Research Conference of the American Psychiatric Association held under the auspices of Syracuse University in April of 1957. The original version has appeared in print (27) and a modified version is presently in press as one of the Psychiatric Research Reports of the American Psychiatric Association. The full details of this study are therefore not referred to in the present paper. In summary: at the end of 5 months of treatment, 70% of patients, if all diagnostic categories are included, showed some degree of favorable response. If only the patients with functional psychosis are included, 86% showed response with the remaining 14% having been discontinued from medication for a variety of reasons. In view of the fact that average duration of hospitalization of these patients was 20 years with a minimum period of 9 years and that there was failure to respond to all previous therapies these results are quite impressive despite the small number of cases involved.

B. At the end of one month, of the patients given reserpine first who a week later had iproniazid added, 10 had shown no change and 5 only slight improvement. At the end of 8½ months, one of this group had become worse, 6 remained unchanged, 5 had shown improvement to some degree in respect to behavior, 2 had shown some improvement in respect to both behavior and psychological status (such as lessening of delusions) and one had shown moderate improvement in both the behavioral and psychological area.

Of the patients given iproniazid for a week who then had reserpine added to their regimen, at the end of one month, 11 had shown no change and 4 slight improvement. By the end of 8½ months, 3 had become decidedly worse, 6 had shown no change, 5 slight improvement and 1 moderate improvement in respect to both behavior and psychological status.

Review of the individual case histories which follow would seem to indicate that changes in both groups were generally in the direction of increased activity. At times this led to improved behavior but at other times it led to an accentuation of assaultive excited tendencies with the clinical result that the patient became worse. The increased activity (for better or for worse) appears to be greater in the group pre-treated with iproniazid as seemed likely from the animal experiments. The drug *is not* of general use for the treatment of schizophrenics *per se*. Few of these patients were of the type described in group "A" nor were any of them markedly depressed.

On the basis of other experience both in and out of the hospital at a later date an additional 5 hospitalized patients who *were* characterized by marked depression were then started on iproniazid, 50 mgs. t.i.d., followed one week later by 1 mg. daily of reserpine. All of these patients *without exception* have shown moderate improvement and treatment is continuing except for one patient who developed jaundice 2½ months

after treatment began. It has not been definitely ascertained that the jaundice is drug related but this certainly is a possibility. Even this patient after 2½ months showed moderate improvement which has been maintained after withdrawal of medication. It is our impression that the drug in combination tends to act even more potently than iproniazid alone to increase psychic energy. There is no real evidence however that it alone has an ataraxic effect. This leaves open the possibility of using iproniazid in combination with *ataraxic* doses of either reserpine, one of the phenothiazine derivatives or other demonstrated ataraxics. In a few cases we have done this and the results appear promising. We have also begun using the parenteral form of iproniazid and results in some cases have been seen within one hour.

C. The remarkably high degree of success among the patients treated in private practice is best understood by referring to the individual case histories. The drug must, however, be used for an adequate period of time. The addition of d-amphetamine, as suggested by Spiegel, increases the clinical usefulness since results are much more rapid. In cases where amphetamines are contraindicated the parenteral form of iproniazid may provide an adequate substitute.

One additional observation of considerable interest is that in a number of mild psychoneurotics and in a number of volunteers the use of iproniazid in combination with d-amphetamine has enabled the subjects to continue for as long as six months with an average of 4 to 5 hours sleep a night instead of the customary 8 or 9. This has been done without evidence of side effects and may have important implications. There also exist a great number of possible applications of iproniazid that have yet to be explored. Bosworth has demonstrated the value both in certain post-operative conditions and in terminal diseases.

Scherbel has shown its worth in arthritic patients but in addition to its usefulness in convalescent states it should be tried in geriatric patients, in narcotic addiction (as suggested by Bosworth), in pre-menstrual tension and depression states, and in pediatrics. Its possible value for improving performance in normal individuals should also not be overlooked.

Summary

1. Additional evidence of the value of iproniazid in the treatment of depressed, hypoactive patients is presented.

2. The drug increases psychic energy and this may result in clinical worsening as well as improvement in certain types of mental disease. It does not seem to be an ataraxic but can be used in combination with one.

3. The combination of iproniazid followed a week later by reserpine seems to increase the degree of activity.

4. The addition of d-amphetamine to iproniazid accelerates the action remarkably and makes the treatment much more valuable for office use.

5. A variety of other possible applications are suggested.

APPENDIX

Four typical cases have been selected from among nine private patients tried on iproniazid by one of us (NSK). In two additional cases where response was only partial, 1.0 mg. of reserpine was added at the end of the third week (in one case) and after a month (in the second case). Improvement was accelerated and one of these patients is now ready for discharge.

Case 1. A 30 year old housewife with two children had suffered from severe anxieties and compulsions since the age of 18. She had undergone some seven years of psychoanalytic treatment and had been tried on virtually all of the new tranquilizing drugs as they became available but without any evidence of permanent or marked improvement. In the course of some two years of psychiatric treatment an underlying depression emerged to the surface and she was then started on iproniazid at doses of 50 mgs. t.i.d. Within two to three weeks her depression began lifting and when 5 mgs. of d-amphetamine b.i.d. was added to the regimen, she exhibited a zest and enjoyment of life which had not been evidenced previously. After four months of treatment on this dosage she had found part time employment as a receptionist which she thoroughly enjoyed and has now made application for training in one of the allied medical professions demonstrating a most remarkable reversal in personality. At the end of the fourth month she developed a neuralgia of the ear which necessitated reduction of dosage and the addition of 50 mg. of pyridoxine following which the condition cleared up.

It is interesting to note that despite the rather excruciating pain from the neuralgia she announced in no uncertain terms to the therapist that she desired to continue the treatment with iproniazid even though she would have to have the physical pain the remainder of her life. Fortunately, as indicated, this was not necessary and she is now doing extremely well on a dosage of 10 mgs. once a day.

Case 2: A 48 year old housewife from Canada had been suffering cyclic depressions every two to three weeks for a period of 17 years. She had spent time at some of the leading medical centers of the United States in an attempt to have the condition suitably diagnosed and treated. During her periods of immobilization she was completely unable to get out of bed, took no care of her personal needs and was in the very "slough of despond." The results of previous treatment were sufficient to relieve her of some of the feelings of guilt which accompanied the depression but did not effect the basic condition. The longest period she had ever gone without depression was while under intensive therapy for a period of slightly less than two months. During a visit to New York she appeared for consultation and was seen briefly on three occasions primarily for purposes of diagnosis. After being placed on iproniazid she had to return home. For the next three months she continued without any evidence of recurrence of depression and at the time of this writing had developed an intercurrent medical condition which it was felt indicated the temporary withdrawal of the iproniazid. Her major concern is that the depression may recur but since the condition is relatively self-limited, it is quite possible that the prolonged action of the iproniazid may enable her to carry through the present episode without recurrence of the depression. It is then planned to again return her to a maintenance dose of iproniazid.

Case 3: A young divorced woman in her twenties had been seen four or five years ago for psychotherapy but was a most unresponsive subject. She was characterized by lack of interest in social activities despite her rather attractive appearance and also by chronic anorexia. Recently she returned again for treatment and was given the combination of 50 mgs. of iproniazid t.i.d. and 5 mgs. of d-amphetamine b.i.d. She has, within the first few weeks of treatment, shown a remarkable gain of weight and symptomatic relief of her anorexia and has begun quite active social participation.

Case 4: A Viennese housekeeper in her fifties was referred by an internist who was greatly concerned about her suicidal preoccupations. After two years of intensive therapy her former psychiatrist felt that he could not be of further help to her and had terminated the relationship. In view of a history of two previous suicidal attempts the internist who was caring for her gastrointestinal condition (an ulcer) referred her on an emergency basis. On 50 mgs. iproniazid t.i.d. she developed a fair amount of dizziness and it was necessary after a few days to reduce the dosage to half. She was also given 5 mgs. of d-amphetamine once a day. Within one week her appearance was almost unrecognizable. Her usually furrowed brow and dolorous faces were replaced by such different expression that the present therapist literally did not recognize her when she walked into the office and it required a rapid readjustment to realize that it was the same patient. This particular patient had also been seen by a colleague of the therapist and the same remarkable change was evident to him. She has continued much as after the first weeks of improvement and although she faces some serious psychotherapeutic problems she appears amenable for the first time to establishing the necessary relationship to accomplish such treatment.

Case 5: Dr. Herbert Spiegel[1] describes the patient on whom he made the original observation of the effectiveness of the combination of iproniazid and d-amphetamine, as follows:

This is a 50 year old, married, white, male, Sales engineer, with a history of depression since the age of 17. His youngest sister, 45, is currently a hospitalized schizophrenic. The patient has had five major depressive episodes from the age of 17 to the present, each depression lasting from one year to four years. The current depression is now in its sixth month and as yet has not required hospitalization. With two previous depressions, he was hospitalized and the last depression was severe enough to warrant ECT. He did not respond to the first; during the second ECT he developed respiratory arrest and was considered a poor risk for continuation of therapy. Because of that his family refuses any further use of ECT. His current depression is characterized by lethargy, restlessness, general lack of interest, and recurring complaints about his helplessness. He has been aided in maintaining a limited business activity with the use of d-amphetamine during the day and Sodium Amytal for sleep at night. He was then started on prochlorperazine (Compazine), 60 mg. daily, and after the second day with no apparent effect this was increased to 90 mgs. daily. Two days after this he became much more sluggish, his depression became much more marked and he talked about suicide. The prochlorperazine was promptly stopped and within a day the severity of depression was relieved. After two or three days he returned to the previous level of depression with no indications of suicide.

On January 31, 1957 the patient was started on 50 mgs. of iproniazid t.i.d. The only other medication was Seconal for sleeping. The patient was being seen on a four times a week basis and on February 6 it was noticed that the depression had lifted very slightly. The dosage was then increased by an extra 50 mgs. at breakfast but no further alleviation of symptoms was noted. On February 23, 5 mgs. of d-amphetamine was added to the regimen and within two days the patient was obviously brighter and more animated. This improvement has continued and increased further so that for the first time in nine months the patient is active in his

business. He has even "gone out on the road" selling which he had not done for years previously. On March 4 the dosage of iproniazid was dropped to 100 mgs. a day and at present (June) it has been possible to reduce his psychotherapeutic sessions to two or occasionally three times a week. During the last few months he has been faced with a number of strong environmental and emotional traumas involving the death of one of his parents and the problem of caring for the remaining one. He has been able to make important business decisions which it had been necessary for him to defer in the past and also to manage a fairly complicated and unpleasant domestic relationship. Seconal is no longer necessary for sleeping with an occasional dose of chlorohydrate being the only hypnotic.

Case 6: The four following case summaries are selected from the fifteen patients Dr. Samuel Sandler[2] has treated. Among the fifteen there was only one patient who failed to respond satisfactorily although there are mitigating circumstances.

A previously very independent business woman married a few years ago and at the age of 47 developed hypertension, a cardiac condition and a hemiplegia. This led to a marked depression with extreme discouragement and hostility. Six months spent at a "retraining" institution ended in failure which led to her being referred for psychiatric treatment. The possibility of electroconvulsive therapy was considered but was discouraged by the consulting cardiologist. Three months of psychotherapy proved fruitless and therefore when iproniazid became available she was immediately given 50 mgs. t.i.d. At the end of three weeks the patient had improved sufficiently to describe herself as feeling "pretty good." Progress continued at a very satisfactory pace and now for the first time in two years since her hemiplegia she accepts her life situation, is active about the house and has regained the cheerfulness and gaiety which characterized her in the past.

Case 7: A housewife in her early fifties developed reactive depression following the death of her mother. She was unable to do any housework, did not see her neighbors and had no interest in her family. Following a course of electroconvulsive therapy she showed slight improvement but relapsed within one month. There seemed no alternative but institutionalization. The availability of iproniazid offered a possible alternative and she was started on 50 mgs. t.i.d. Improvement became evident after two or three weeks of treatment and at the end of 2½ months she spontaneously remarked, "My whole life has been reversed." Instead of fearing each day she looks forward to all the pleasures it will bring.

Case 8: A 50 year old bachelor employed as an important official of a well known organization had suffered intermittent depressions for the past 30 years. In order to make it possible for him to continue at all he had been receiving maintenance electroconvulsive therapy every three months. A few weeks prior to the present treatment he developed a heart condition which had to be taken into consideration when his depression recurred. The use of ECT was considered dangerous. His response to iproniazid occurred within a week and at the present time he states, "It seems to be the answer to my problem after 30 years of searching." He had also been apprehensive because he felt that his cardiac status might lead to his death if he exerted himself unduly. During a recent session he commented with surprised satisfaction on the fact that he had had sex relations *twice* the evening before, a physical exertion which he had believed was no longer possible.

Case 9: A 45 year old Italian housewife developed an involutional depression precipitated by the necessity of committing her sister to an institution (also because of depression). She withdrew to the extent that she did not visit her parents, would not eat or sleep, losing 20 pounds as a result. She was given a course of electroconvulsive therapy with considerable improvement but this was maintained no longer than three weeks. During the next four months of treatment her depression continued to deepen and plans for institutionalization had already been made when iproniazid was given. Within three weeks she began to smile occasionally during her visits. She is now considerably improved having gained back some of her weight, is sociable again and has a much more optimistic attitude.

Case 10: Dr. Beatrice Nachtigal[3] reports the following experience:

A 42 year old decompensated schizophrenic woman with three children was obsessed with the thought of poisoning her family and was much upset by these ideas. In a first episode in her twenties she was ill for two years with the same preoccupations and was supported by family reassurance rather than formal treatment. When in her thirties there was a recurrence of a similar episodes which terminated abruptly when she broke her ankle. The third episode occurred some 5 years ago during which she was given 10 to 15 electric shock treatments which brought about some respite although she was not returned to anything like functional capacity until she had undergone 9 months of additional psychiatric treatment. The present episode was as described above and she had been seen for three weeks before treatment with 50 mgs. of iproniazid and 5 mgs. of d-amphetamine t.i.d. were started. At the end of one week she had shown gradual improvement in respect to the fact that she now felt she had sufficient courage to "lick" her illness without the necessity of either hospitalization or electroconvulsive therapy. Previously she had pleaded for any treatment that would relieve her in any way.

As her assurance that she could deal with the illness increased, the thoughts and ideas became more overt and she raised the question as to whether she ought not to carry out her obsession. By facing her directly with the reality situation and the probability that such behavior would result in legal punishment as well as *real* guilt, she was able

to reject the idea of such "acting out." She came to understand that her real problem lay elsewhere and that the death wishes against the children actually referred back to her own childhood. Following this episode which occurred about one month after starting iproniazid she began getting better and was able to explore her various relations with people. At the present time, although on rare occasions, these thoughts return she is able to brush them off with great ease. The dosage is presently being reduced.

Case 11: Following announcement of our results in April at the American Psychiatric Association Regional Research Conference in Syracuse, N. Y., many inquiries followed. Those from private individuals were answered by referring them to their family physicians. In one case, among others, the general practitioner obtained a draft of our paper and was brought up to date on our most recent results and techniques. He started a case on medication in mid-April. On June 6 the patient wrote again and parts of her letter were as follows: "You see, doctor, the pills have worked. . . . I am not depressed or frightened any more. I go everywhere and talk to everyone. I am full of energy. . . . I used to force myself to sleep until 1:00 P.M. because I knew the day would be like any other. Dull and empty and at times frightening. Now I am up at six and can't wait to get started cleaning my home, painting and decorating it. After my work I go visiting or take my nephews fishing in the park. The day now seems too short. Not long enough for all the things I want to do. . . . To me it seems like a miracle, for I knew that I was in for another year of depression. I shall be eternally grateful."

Case 12: Dr. Edward L. Croxdale[4] of Villisca, Iowa, was also among those who requested specific techniques and in a letter dated June 6 he writes, in part: "I felt you might be interested to know I was anxious to try the drug on a 48 year old male who had a severe depression. In August and September of 1955 he . . . received shock therapy with some improvement. However during the past year he gradually became worse. He has been on Thorazine, 25 mg. t.i.d. and Equinal, 400 mg. t.i.d., with so-so results. We started Marsilid, 50 mg. t.i.d., and maintained the dosage of the other drugs. His wife tells me she noticed no change for about three weeks. After that she noticed a gradual change, his depression now after six weeks is gone. His outlook on life is normal and wholesome." In addition the patient had been diagnosed in 1950 as having amyotrophic lateral sclerosis and the iproniazid did not produce any increase in muscular weakness, nor was there any unsteadiness of gait, etc.

Case 13: Dr. Mortimer Ostow[5] is preparing for publication the description of an intensely studied case; that of a 53 year old man in a fairly profound reactive depression. The psychoanalysis was extremely stormy and there was real apprehension lest the patient kill himself. In view of this circumstance he was given iproniazid, 50 mg. t.i.d., and improvement was seen within 10 days. The psychodynamic changes were extremely interesting. After the patient was relieved of his depression, the drug was reduced and after each dose reduction changes were again observable. Medication has now been completely withdrawn.

Authors' Note: The iproniazid used in this study was supplied by Hoffmann-LaRoche, Inc., Nutley, New Jersey, under the name Marsilid.

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Errors in Judgment When Fased with an "Affront"

EDMUND BERGLER, M.D.

Some people admit it; some do not—but Boswell's dictum, "My favorite topic, myself," applies to everyone. Too much concentration on self has many disadvantages, but only one facet will be singled out here: the errors in judgment that invariably arise when a person is subjected to an "affront." The core of such errors consists of starting one's deliberations with the indignant question: "How can he do this to *me*?" Thus, one's own lovable self becomes the primum movens.

Placing the accent on oneself automatically renders these deliberations worthless. Doing so bypasses the fact that the other fellow (the offender) uses the identical priority list, and therefore places *himself* on top. A matter that should be explained in terms of the other fellow's needs and motivations is consequently twisted into a personal problem of self. This "little error" has far-reaching after effects: the entire deliberation ends with a faulty conclusion. It is as though a person worked on a complex mathematical problem, having started his calculation with the unobserved error: 1 plus 1 equals 27.

Mr. A., a writer, made a luncheon appoint-

ment with his literary agent. The specific day, the specific hour, the specific restaurant had been set, and confirmed by letter. The agent did not appear. A. waited one hour, getting more and more furious, and dwelling on the personal affront. He was so angry that he did not even call the agent's office; he preferred to indulge in self-pity and compensatory revenge fantasies. It was not until late in the afternoon that he telephoned the agent's office, only to learn that the agent was ill and at home in bed. Mr. A. had the impression that the secretary at the other end of the line had been expecting his call; he thought her replies and regrets too pat to be true. He had asked why he had not been told of the agent's illness in the morning; he viewed with suspicion the secretary's apologetic explanation that she had forgotten to check the agent's appointments and therefore should be blamed. A. was so furious that he did not even ask the obvious question: had the agent told her to check his appointments?

The next day he received a letter of apology in which the agent put the blame squarely on the inefficiency of his office staff. In discussing the incident during his analytic appointment, A. complained bitterly of the affront and—probably with justification—declared that the "forgetting" was the agent's fault, not his secretary's. However, instead of shrugging his shoulders over the nuisance-value of the incident, and simply asking himself whether he would be better off with another agent than with this one, he delivered a long, masochistic tirade on how meanly "poor little me" was being treated.

"He wouldn't dare if my books were selling like Hemingway or Mike Spillane!"

"Aren't you misusing the incident for self-reproaches over your moderate success?"

"Isn't that unavoidable?"

"Of course it's avoidable. Your inner conscience is on the warpath, and you're being a sucker, playing its game, instead of counteracting it."

"I still say it's a personal affront, a slap in the face!"

"Let's see. Is your agent antagonistic toward you?"

"That's the strange thing: he isn't. But unconsciously he must hate my guts. Otherwise he wouldn't have forgotten."

"Why do you overstress yourself in this incident? What appears like a personal affront may have reasons totally unrelated to you."

"Such as?"

"Not knowing the man, I can only speculate. Perhaps he was in a masochistic mood, unconsciously wanting to make trouble for himself. Perhaps he had to swallow too much nonsense from one of his best-selling clients, and in active repetition of a passively endured experience (a repetition in reverse) took it out on you. Or maybe he had a domestic conflict. Who knows?"

"But I am the injured party!"

"That is quite true. But it doesn't change the fact that the 'affront' may have reasons unconcerned with yourself. You committed not one, but two cardinal errors: First, you began your train of thought with yourself, not the agent. Second, you misused the incident for a masochistic fiesta, thus shortchanging an attack of the inner conscience (superego). And the superego in its turn misused the situation to administer a severe beating to you."

Miss B., an intelligent woman, was executive assistant to an industrialist. During one appointment, she complained bitterly about her boss: all day, she declared, his behavior had been "impossible and insulting." Although the man was in general a rather pleasant and considerate person, she took his ill-humor personally. I asked whether he had treated everyone badly, or had singled her out as the target of his "impossible" behavior. She admitted that it had been a terrible day for everyone coming in contact with him; he had "kicked all of us around."

"Why do you take it personally?" I asked.

"What is that supposed to mean? He mistreated me, didn't he?"

"But if the reason for his extraordinary behavior —which affected everyone he came in contact with —had nothing to do with you, why not make allowances?"

Miss B. then told of an incident that had added fuel to her indignation. She had overheard her boss speaking to his wife on the telephone during the morning. He had catered to his wife in the most humiliating manner. The theme song of his end of the conversation was, "Yes, darling; of course, darling." Miss B. concluded: "At the same time, he was acting the big shot with me!" It seemed likely, from this evidence, that her boss had been through a severe domestic conflict the preceding night, and had not cut a heroic figure in that crisis. To counteract his passivity at home, he exhibited aggression in the office.

Why didn't the intelligent patient see

through that banality? Why did she start the "explanation" with herself? Why was she full of self-reproach—dictated by inner conscience? If she had understood the reasons for her employer's behavior, she would have deprived herself of a good case of injustice collecting.

In short, an emotional situation such as that faced by a person who has met with an "affront" obscures factual thinking. If it did not, the starting point for the individual's subsequent attitude would be placed where it belongs: with the perpetrator of the injury. Equally typical is the fact that the inner conscience seizes the opportunity for a second installment of punishment, and that the victim usually—unconsciously—misuses the attack for the purpose of injustice collecting, hence psychic masochism.

One has to accept the dreary truth that people unconsciously misuse one another for the sake of solving their inner conflicts. The practical consequences that follow such misuse pose another—and again a practical—problem. But knowledge can help the individual who is not too severe a psychic masochist to escape the double pitfall described above.

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The Electroencephalogram of Multiple Sclerosis

(A Preliminary Report)

JAMES B. FUNKHOUSER, M.D., and BENEDICT NAGLER, M.D.

The literature of electroencephalography in multiple sclerosis is sparse enough to permit a brief review. Berger in 1931 reported that abnormal records were found in multiple sclerosis only when there was severe mental change.[1] Lamere confirmed this finding in 1936.[2] Table I summarizes recent reports including the Veterans Administration Cooperative Study.

TABLE I

Senior Author	Number of Cases	Normal	Abnormal		Percent Abnormal
Gibbs[3]	3	2	1	(?)	33
Freeman[4]	6	5	1	(late normal)	16
Hoeffer[5]	107	60	47		44
Strauss[6]	70	66	4		5
Zeifert[7]	34	13	21		62
Booth[8]	79	41	38		48
Scheinberg[9]	20	10	10		50
Fuglsang-Frederiksen[10]	74	12	52		70
VA. Coop. Study	196	86	106		55

Strauss,[6] singularly, reported 66 of 70 cases to have normal records. He found normal records during active phases of the disease, as well as during remissions. He could find no difference in EEG abnormality in the predominantly involved system, whether it was cerebral hemispheres, the cerebellum, brain stem or spinal cord. It was his conclusion, on the basis of small percentage of abnormality found, that an abnormal electroencephalogram casts doubt on the diagnosis of multiple sclerosis and he stated that when the diagnosis of multiple sclerosis is considered and an abnormal electroencephalogram is found the case should be scrutinized more closely in order to make sure that one is not dealing with another disease of the nervous system. Personal communication from Booth[8] is shown on Table I as well as the material of Fuglsang-Frederiksen.[10] The latter three studies and Hoeffer[5] are compared with our findings. In 192 cases in the VA Cooperative Study with one or more EEG's, there were only 86 which were completely and always normal; 106 cases had at least one abnormal record at some time during the study.

It is apparent that there are great differences in the percentages of abnormality obtained by different investigators. The basic question, of course, is what to regard as normal and abnormal. Strauss, for example, did not consider Gibbs' one case abnormal, nor did he consider Freeman's case abnormal be-

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cause it later changed into a normal record.[6] If a given case has both an abnormal and a normal record, how should it be counted statistically?

It is of considerable importance in the undertaking of the difference in Table I to realize that with the VA study, in Hoeffer's report and with Fuglsang-Frederiksen's report (where the largest percentages of abnormality were found), serial records were made. Our records were made at monthly intervals throughout a period of a year. Of course, many cases were dropped out of the study and in some instances only one electroencephalogram was made. These facts introduce murkiness into some aspects of the analysis to follow. We cannot claim ours is a completely serial study, nor can we say, for example, that some of our 86 cases which were always normal, would not have become abnormal if we had made a few more (or even one more) record. All of our cases did not have exactly 12 electroencephalograms.

Our report is the "by-product" of a larger study of multiple sclerosis initiated and conducted by the Department of Neurology of the Veterans Administration. It had been reported by Kurtzke and Berlin[11] that isonicotinic hydrazine (INH) was beneficial in the treatment of multiple sclerosis. To check this a double-blind placebo study was applied to the study of INH in the treatment of multiple sclerosis in 11 widely separated stations of the Veterans Administration where there were qualified neurologists for responsible investigators. INH was administered, 100 mgms, three times a day, to certain cases of multiple sclerosis that had been rigidly selected, to make a "pure" group. The primary purpose was to determine whether or not INH would modify the symptoms or findings of multiple sclerosis. A neurological examination, spinal fluid, psychological and electroencephalographic studies were made at regular intervals throughout the period. This is a preliminary report of the EEG's. Other aspects were reported elsewhere.[12,13]

In the course of our study 1127 electroencephalograms were made on 192 patients. Initially these electroencephalograms were interpreted at the individual stations; 853 of the EEG's were later reviewed by the authors of this report in an effort to obtain consistency of interpretation. They were divided into normal, abnormal, and borderline normal.

Though it is admitted that for accurate scientific purposes, there is lack of uniformity in the making and interpretation of these records, the case material is, we believe, as strict as could possibly be arranged. In the first place the design of the primary study required that a reasonable certainty of diagnosis of multiple sclerosis be established. For inclusion in the study, it was necessary for the patient to have had the onset of the disease between the ages of 18 and 45. He had to have past or present evidence of simultaneous involvement on the part of two or more areas of the central nervous system. There must have been an acceptable history of at least two episodes of signs or symptoms of multiple sclerosis or a history of a slowly progressive lesion of the central nervous system over a period of six months or more.

Excluded were all cases where a diagnosis of multiple sclerosis was in doubt, such as those of acute encephalitis, vascular lesions or syphilis. Excluded also were those with a history of epilepsy. The reason for this last exception was that experience with INH in tuberculosis had suggested that the drug was capable of potentiating latent epilepsy. The removal of known epileptics from the series probably has decreased the percentage of paroxysmal (and thus abnormal) EEG's obtained. Only 10 cases had paroxysmal records (5.2%). Only three patients developed seizures under treatment, one of these while taking the placebo. It does not appear, therefore, that INH in the dosage we employed is very potent in the activation of epilepsy.

In comparing the initial electroencephalogram with those at the termination of treatment, there was no evidence of any change in the rate, amplitude or character of the record as a result of the INH. Wingeld[12] states that in a serial EEG study of 52 patients who were receiving INH for pulmonary tuberculosis, there were no observable changes in the 166 electroencephalograms as compared with the normal or abnormal records prior to therapy.

TABLE II

	3 Mos.		6 Mos.		9 Mos.		12 Mos.	
Change	P	INH	P	INH	P	INH	P	INH
Improved	6	2	3	6	4	4	5	3
Unchanged	51	49	46	38	33	29	22	18
Worse	10	9	8	8	4	8	3	9
Total	67	60	57	52	41	41	30	30

Table II shows the change in EEG interpretations between enrollment and follow-up at quarterly intervals. There is no significant alteration in the EEG's as the result of the treatment.

TABLE III

	EEG Interpretation			
Predominant Source of Incapacity	Total	Normal	Borderline	Abnormal
Total	176	121	23	32
Cranial Nerve	6	5	—	1
Incoordination	36	23	7	6
Weakness	58	39	9	10
No single area	76	54	7	15

Table III shows there were no significant relationships of encephalographic abnormality to either cranial nerves, coordination, weakness, or where no system was predominantly involved.

An effort was made to compare EEG abnormality with clinical dysfunction as rated by what is called the Bronx Scale. In the Bronx Scale a rating of 1 is minimal disability, 5 moderate, 9 severe. Table V shows that EEG abnormality is not related to severity of symptoms.

Our record confirmed the usual abnormality in multiple sclerosis to be in a diffuse 5 to 8 per second slowing, particularly in the frontal areas, sometimes limited to one side of the head and sometimes focal, not continuous nor paroxysmal as a rule, but a random, irregular, slowing. This has already been reported by many authors starting with Berger. We have learned that INH does not modify the EEG in multiple sclerosis in clinical dosages. We have confirmed the findings of others that the EEG abnormalities

TABLE IV

	EEG Interpretation			
	Total	Normal	Borderline	Abnormal
Total	1,021	666	153	202
Cranial—Normal	287	186	42	59
Psychiatric Normal	253	165	38	50
Psychiatric Abnormal	34	21	1	9
Cranial—A1	307	217	36	54
Psychiatric Normal	257	189	25	43
Psychiatric Abnormal	50	28	11	11
Cranial—A2	427	263	75	89
Psychiatric Normal	277	178	41	58
Psychiatric Abnormal	150	85	34	31
	PERCENT			
Total	100.0	65.2	15.0	19.8
Cranial—Normal	100.0	64.8	14.6	20.6
Psychiatric Normal	100.0	65.2	15.0	19.8
Psychiatric Abnormal	100.0	61.8	11.8	26.5
Cranial—A1	100.0	70.7	11.7	17.6
Psychiatric Normal	99.9	73.5	9.7	16.7
Psychiatric Abnormal	100.0	56.0	22.0	22.0
Cranial—A2	100.0	61.6	17.6	20.8
Psychiatric Normal	100.0	64.3	14.8	20.9
Psychiatric Abnormal	100.1	56.7	22.7	20.7

A1 is the involvement of the optic nerve only; A2 is involvement of the cranial nerves other than optic (although the optic may be also involved).

No significant relation of EEG abnormality to any of the cranial nerves or psychiatric symptoms can be seen in Table IV.

TABLE V

Kurtzke[15] Scale Rating	EEG Interpretation			
	Total	Normal	Borderline	Abnormal
Total	176	121	23	32
1-5	72	50	9	12
6-9	104	71	14	19

in multiple sclerosis do not match well with clinical findings nor with severity of symptoms nor with mental change.

Whether to assign differential diagnostic value to an abnormal electroencephalogram found in a possible case of multiple sclerosis will depend on how the individual interprets records. For example, Strauss, who found 5% of his records abnormal, was quite justified in considering that an abnormal EEG would cast doubt on the diagnosis of multiple sclerosis; and Gibbs[13] was undoubtedly correct in stating, on the basis of his find-

ings, that an abnormal EEG would favor a diagnosis of acute encephalitis over multiple sclerosis in questionable cases.

However, if you are willing to accept the higher percentage of abnormality found in studies similar to ours, you would not wish to attach any diagnostic significance to either a normal or abnormal brain wave in a case suspected of multiple sclerosis. Since our data would tend to show that if serial electroencephalograms are made, slightly more cases of multiple sclerosis will show abnormality than not.

Schwab[14] has commented that the EEG has some value in differentiating a localized spinal lesion due to trauma, tumor or infection from a suspected case of multiple sclerosis. He said the presence of an abnormal rhythm in the EEG would point to involvement of cerebral structures and suggest multiple sclerosis in such a case since a pure *spinal* case would not show EEG abnormality. Our statistics so far cannot completely support this contention. We will have to review our material on this point. Also, though implied in our tables, it is not certain whether abnormality is present only during clinical exacerbation (as considered by Freeman).

Summary

The EEG findings are reported in 192 cases of multiple sclerosis who had no prior history of epilepsy. Some of these were treated by INH. INH does not influence the EEG in multiple sclerosis. EEG abnormality does not seem to relate to severity of symptoms, nor to the predominant system involved, nor to mental symptoms in multiple sclerosis. The usual abnormality is a random, irregular slowing 5 to 8 per second, diffuse and shifting, but particularly in frontal areas. One hundred and six, or 55%, of our cases at some time or another showed an abnormal tracing. This is a much higher figure of abnormality than is usually reported and would seem to demonstrate the obvious—namely, that when serial electroencephalograms are made, more abnormality is found. Because of this the differential diagnostic value of one electroencephalogram in a case of multiple sclerosis seems small unless it is correlated with the clinical neurological findings.

Authors' Note: This study has been reviewed in the Veterans Administration and is published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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VALERIANETS-DISPERT are indicated in cases of nervous excitement and exhaustion, anxiety and depressive states, cardiac and gastrointestinal neuroses, menopausal and menstrual molimena, insomnia.

Dose: 1 or 2 tablets t.i.d — Bottle of 50 and of 100 tablets

At All Prescription Pharmacies

STANDARD PHARMACEUTICAL CO., INC., • 253 West 26th St., New York

For Intestinal Dysfunction
NUCARPON®
Each tablet cont: Extract of Rhubarb, Senna, Precip. Sulfur, Peppermint Oil, Fennel Oil in activated charcoal base

For making Burow's Solution U.S.P. XIV
WET DRESSING Use
PRESTO-BORO®
(Aluminum Sulfate and Calcium Acetate)
POWDER IN ENVELOPES
— TABLETS —
For treatment of Swellings, Inflammations, Sprains

For Pulmonary Conditions
TRANSPULMIN®
3% solution Quinine with 2½% Camphor for Intramuscular Injection.

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